# Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development

Regev, Arie ; Avigan, Mark I ; Kiazand, Alexandre ; Vierling, John M ; Lewis, James H ; Omokaro, Stephanie O ; Di Bisceglie, Adrian M ; Fontana, Robert J ; Bonkovsky, Herbert L ; Freston, James W ; Uetrecht, Jack P ; Miller, Ethan D ; Pehlivanov, Nonko D ; Haque, Syed Asif ; Harrison, Melanie J ; Kullak-Ublick, Gerd A ; Li, Hewei ; Patel, Niti N ; Patwardhan, Meenal ; Price, Karen D ; Watkins, Paul B ; Chalasani, Naga P

Abstract: Immune checkpoint inhibitors (ICIs) have shown significant efficacy in patients with various malignancies, however, they are associated with a wide range of immune-related toxicities affecting many organs, including the liver. Immune-mediated liver injury caused by checkpoint inhibitors (ILICI) is a distinctive form of drug induced liver injury (DILI), that differs from most DILI types in presumed underlying mechanism, incidence, and response to therapeutic interventions. Despite increased awareness of ILICI and other immune-related adverse effects of ICIs reflected by recent guidelines for their management in post marketing clinical practice, there is lack of uniform best practices to address ILICI risk during drug development. As efforts to develop safer and more effective ICIs for additional indications grow, and as combination therapies including ICIs are increasingly investigated, there is a growing need for consistent practices for ILICI in drug development. This publication summarizes current best practices to optimize the monitoring, diagnosis, assessment, and management of suspected ILICI in clinical trials using ICI as a single agent and in combination with other ICIs or other oncological agents. It is one of several publications developed by the IQ DILI Initiative in collaboration with DILI experts from academia and regulatory agencies. Recommended best practices are outlined pertaining to hepatic inclusion and exclusion criteria, monitoring of liver tests, ILICI detection, approach to a suspected ILICI signal, causality assessment, hepatic discontinuation rules and additional medical treatment.

DOI: https://doi.org/10.1016/j.jaut.2020.102514

Regev, Arie; Avigan, Mark I; Kiazand, Alexandre; Vierling, John M; Lewis, James H; Omokaro, Stephanie O; Di Bisceglie, Adrian M; Fontana, Robert J; Bonkovsky, Herbert L; Freston, James W; Uetrecht, Jack P; Miller, Ethan D; Pehlivanov, Nonko D; Haque, Syed Asif; Harrison, Melanie J; Kullak-Ublick, Gerd A; Li, Hewei; Patel, Niti N; Patwardhan, Meenal; Price, Karen D; Watkins, Paul B; Chalasani, Naga P (2020). Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development. Journal of autoimmunity, 114:102514.
DOI: https://doi.org/10.1016/j.jaut.2020.102514

Journal of Autoimmunity 114 (2020) 102514

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

# Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development☆

Arie Regev[a,*], Mark I. Avigan[b], Alexandre Kiazand[c], John M. Vierling[d], James H. Lewis[e], Stephanie O. Omokaro[b], Adrian M. Di Bisceglie[f], Robert J. Fontana[g], Herbert L. Bonkovsky[h], James W. Freston[i], Jack P. Uetrecht[j], Ethan D. Miller[k], Nonko D. Pehlivanov[l], Syed Asif Haque[c], Melanie J. Harrison[m], Gerd A. Kullak-Ublick[n], Hewei Li[o], Niti N. Patel[p], Meenal Patwardhan[q], Karen D. Price[r], Paul B. Watkins[s], Naga P. Chalasani[t,**]

[a] Eli Lilly, Indianapolis, IN, USA
[b] US Food and Drug Administration, Silver Spring, MD, USA
[c] AstraZeneca Pharmaceuticals, Gaithersburg, MD, USA
[d] Baylor College of Medicine, Houston, TX, USA
[e] Georgetown University, Washington, DC, USA
[f] Saint Louis University, St. Louis, MO, USA
[g] University of Michigan, Ann Arbor, MI, USA
[h] Wake Forest University, Winston-Salem, NC, USA
[i] University of Connecticut, Stamford, CT, USA
[j] University of Toronto, Toronto, ON, Canada
[k] MD Anderson, Houston, TX, USA
[l] Janssen Pharmaceuticals, Titusville, NJ, USA
[m] Bristol-Myers Squibb, Lawrenceville, NJ, USA
[n] Novartis, Basel, Switzerland, and University Hospital Zurich, University of Zurich, Zurich, Switzerland
[o] Bristol-Myers Squibb, Lawrenceville, NJ, USA
[p] Takeda, Cambridge, MA, USA
[q] AbbVie, Chicago, IL, USA
[r] Bristol-Myers Squibb, New Brunswick, NJ, USA
[s] University of North Carolina, Chapel Hill, NC, USA
[t] Indiana University School of Medicine, Indianapolis, IN, USA

ARTICLE INFO

*Keywords:*
Immune-mediated liver injury
Immunotherapy
Checkpoint inhibitors

ABSTRACT

Immune checkpoint inhibitors (ICIs) have shown significant efficacy in patients with various malignancies, however, they are associated with a wide range of immune-related toxicities affecting many organs, including the liver. Immune-mediated liver injury caused by checkpoint inhibitors (ILICI) is a distinctive form of drug induced liver injury (DILI), that differs from most DILI types in presumed underlying mechanism, incidence, and

*Abbreviations:* AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; ATG, anti-thymocyte globulin; ATs, aminotransferases; CK, creatine kinase; CMV, cytomegalovirus; CTP, Child Turcotte Pugh; CSs, corticosteroids; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DBL, direct bilirubin level; DILI, drug induced liver injury; EBV, Epstein-Barr virus; ESMO, European Society for Medical Oncology; FDA, United States Food and Drug Administration; GGT, gamma glutamyl transferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; ILICI, immune mediated liver injury caused by immune checkpoint inhibitors; INR, international normalized ratio; IQ, the International Consortium for Innovation and Quality in Pharmaceutical Development; IWG, Immunotherapy Working Group; irAEs, immune related adverse events; HSV, herpes simplex virus; NCCN, National Comprehensive Cancer Network; NSCLC, nonsquamous non-small-cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PT, prothrombin time; SITC, Society for Immunotherapy of Cancer; TBL, total bilirubin level; ULN, upper limit of normal

☆ Disclaimer: The views expressed in this publication are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US Food and Drug Administration or the US Government.

* Corresponding author.
** Corresponding author.
*E-mail addresses:* regev_arie@lilly.com (A. Regev), nchalasa@iu.edu (N.P. Chalasani).

https://doi.org/10.1016/j.jaut.2020.102514
Received 26 June 2020; Accepted 7 July 2020
Available online 05 August 2020

Drug-induced liver injury
Drug-development

response to therapeutic interventions. Despite increased awareness of ILICI and other immune-related adverse effects of ICIs reflected by recent guidelines for their management in post marketing clinical practice, there is lack of uniform best practices to address ILICI risk during drug development. As efforts to develop safer and more effective ICIs for additional indications grow, and as combination therapies including ICIs are increasingly investigated, there is a growing need for consistent practices for ILICI in drug development. This publication summarizes current best practices to optimize the monitoring, diagnosis, assessment, and management of suspected ILICI in clinical trials using ICI as a single agent and in combination with other ICIs or other oncological agents. It is one of several publications developed by the IQ DILI Initiative in collaboration with DILI experts from academia and regulatory agencies. Recommended best practices are outlined pertaining to hepatic inclusion and exclusion criteria, monitoring of liver tests, ILICI detection, approach to a suspected ILICI signal, causality assessment, hepatic discontinuation rules and additional medical treatment.

## 1. Introduction

Experimental analysis of checkpoint signaling pathways involving primarily the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1) receptor and programed death ligand-1 (PD-L1) has elucidated their important role in tumor-induced immune suppression and led to rapid progress in immunotherapeutic approaches to cancer treatment [1,2]. To date, 7 immune checkpoint inhibitors (ICIs) have been approved for clinical use, including the CTLA-4 inhibitor ipilimumab, the PD-1 inhibitors nivolumab, pembrolizumab, and cemiplimab and the PD-L1 inhibitors atezolizumab, avelumab, and durvalumab [2–4]. ICIs have led to significant increases in survival and/or response rates of patients with a variety of tumors, including advanced nonsquamous non-small-cell lung cancer (NSCLC), melanoma, renal cell carcinoma, squamous cell carcinoma of the head & neck, urothelial carcinoma, colorectal carcinoma, gastric carcinoma, hepatocellular carcinoma (HCC), Merkel cell carcinoma and Hodgkin's lymphoma [2,3,5]. However, these survival benefits come with a cost of immune-related adverse events (irAEs) affecting a variety of organs. These include, but are not limited to, infusion-related reactions, skin rashes, colitis, hepatic injury, pneumonitis, pericarditis, myocarditis, uveitis, and a number of different endocrinopathies [2,6–9].

Immune-mediated liver injury caused by ICIs (ILICI) (pronounced as “il-lis-e”) is a well-recognized irAE associated with ICIs and is a concern for patients, healthcare providers and the drug industry. ILICI is a unique type of drug-induced liver injury (DILI), which generally differs from other types of DILI with respect to its suspected underlying mechanism, incidence, clinical manifestations and response to immunosuppression. As recently suggested by Hoofnagle and Björnsson [10], ILICI represents an example of a third type of DILI, which differs from idiosyncratic and direct hepatotoxicity, and is caused by an indirect effect of ICIs on the liver by virtue of their immune-mediated mechanism of action. ILICI may range in severity from mild, asymptomatic elevations of serum aminotransferases (ATs) to acute liver failure [11–16]. Furthermore, combination therapies, of 2 ICIs or ICIs and other chemotherapies, which are commonly used in cancer patients, may have synergistic adverse effects which can significantly increase the risk of liver injury [17,18].

Early detection and management of ILICI during drug development and post marketing are essential, given the potential adverse impact on clinical outcome. Despite increasing knowledge and understanding of irAEs caused by ICIs, there are no consistent practices regarding the monitoring, diagnosis, assessment, and management of ILICI during drug development. Although multiple societal, regulatory and investigator generated publications have proposed a variety of approaches to assessment and management of suspected ILICI, they have been inconsistent in several important areas, forcing drug developers to choose among conflicting recommendations when designing clinical trials using ICIs [2,6–9,19–21].

The IQ DILI Initiative was launched in June 2016 within the International Consortium for Innovation and Quality in Pharmaceutical Development (also known as the IQ consortium) to attain consensus and to propose best practices on topics related to clinical DILI [22]. The IQ Consortium is a science-focused, not-for-profit organization addressing scientific and technical aspects of drug development. It is comprised of over 40 pharmaceutical and biotechnology companies. The IQ-DILI Initiative is an affiliate of the IQ Consortium, comprised of representatives from 18 IQ member companies. The purpose of IQ DILI is to establish evidence-based best practices for diagnosing, monitoring, managing, and preventing DILI.

This publication is based on an extensive literature review, a survey of current approaches used by IQ DILI members, and consensus achieved through structured discussions among IQ DILI members and academic and regulatory experts, which together comprised the IQ DILI Immunotherapy Working Group (IQ DILI IWG). This publication focuses on liver injury caused by ICIs, which constitute the most commonly used agents for cancer immunotherapy to date. Other categories of cancer immunotherapy, such as cytokine treatment, drugs that enhance cytokine production, costimulatory receptor agonists, oncolytic viruses, anti-tumor vaccines, and adoptive cell transfer are not discussed. Of note, most of the data, and recommendations that are included in this publication are specific for acute hepatocellular ILICI. However, ILICI may present as mixed or cholestatic liver injury in a significant minority of affected patients [23–26]. Because of scarcity of data in the published literature to inform best practices regarding the evaluation and management of the cholestatic type of ICI associated liver injury, cholestatic ILICI, is only briefly discussed. Nevertheless, drug developers and investigators must remain mindful of this less common type of liver injury during ICI development and post marketing use.

## 2. Terminology

### 2.1. Commonly used terms

The terminology used to describe hepatic events related to ICIs, has been largely inconsistent. Terms used in published literature include: “immune-related (or mediated) liver injury”, “immune-related (or mediated) hepatotoxicity”, “Immune-related (or mediated) hepatitis”, “hepatic immune-related adverse events”, “ICI-induced liver injury”, “ICI-associated immune-mediated hepatitis”, “checkpoint-induced liver injury”, “autoimmune-like hepatitis”, “immune-induced hepatitis”, “dysimmune hepatitis”, “transaminitis” and others [2,7,9,16,18–20,27–34]. Some of these terms imply various underlying mechanisms or specific histological findings, while others remain incompletely defined. The interchangeable use of these may be confusing and difficult to follow. Because of these limitations, it is the consensus of the IQ DILI IWG that “immune-mediated liver injury caused by checkpoint inhibitors” (ILICI) is a preferred and appropriate term to describe this type of injury.

### 2.2. Serum aminotransferase elevation in ILICI

In some publications, any elevations of serum alanine

aminotransferase (ALT) or aspartate aminotransferase (AST) above the upper limit of normal (ULN), were used to define ILICI. This conflicts with current approaches to other types of hepatocellular DILI [35,36]. Indeed, most authorities in DILI agree that mild asymptomatic increases in serum ALT or AST (> 1x to < 3x ULN) in the absence of an elevation in serum total bilirubin level (TBL) are often not specific and may be related to causes such as nonalcoholic fatty liver disease (NAFLD), changes in diet, and vigorous exercise [35–37]. Patients with malignancy often have alternative causes of ALT and AST elevations such as primary liver tumors, hepatic metastasis, intra- or extra-hepatic biliary obstruction, systemic infection, sepsis, systemic immune-related syndrome, congestive heart failure and concomitant medications [38]. Furthermore, mild elevations in ALT or AST, even if drug induced, may be transient and spontaneously revert to baseline even when therapy is continued, an occurrence often referred to as "adaptation" [35,36,39]. Consistent with this phenomenon, most cases with transient mild asymptomatic elevation of ALT > 1x ULN to < 3x ULN induced by ICIs, without elevation of serum TBL, do not represent clinically significant cases of ILICI, and are more accurately referred to as "elevations in serum ATs".

### 2.3. Use of histological terminology in the absence of a liver biopsy

Since information regarding histological findings in patients with ILICI is still limited, broad use of histology-based terminology is not recommended pending a larger body of evidence. For example, the use of the term "hepatitis" in patients with ILICI (e.g., "ICI-associated hepatitis" or "immune-mediated hepatitis") is appropriate only when diagnosed based on histological examination. This is in keeping with the Council for International Organizations of Medical Sciences (CIOMS) guidelines [40]. In the absence of a liver histology, the term ILICI is preferred.

In ILICI cases with a biochemical pattern consistent with cholestatic liver injury, i.e., predominantly elevated serum alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) with R ratio < 2, the IQ DILI IWG recommends "cholestatic ILICI" as the preferred term. Terms like "ICI-related cholangitis", "ICI-induced cholangitic liver disease" or "biliary pattern hepatitis", which have been used variably in the literature, should be reserved for cases with histological findings or other reliable diagnostic tests (e.g., cholangiography) that are supportive of these terms [23–25].

### 2.4. Liver dysfunction and liver failure

Terms such as "liver dysfunction" and "liver failure", have been used to describe cases of ILICI in the published literature. However, these cases often do not exhibit true abnormal synthetic liver function, but instead are based on isolated elevation of serum ATs. Clinical and regulatory guidelines recommend these terms be reserved for cases with evidence of decreased liver function based on elevated serum levels of direct bilirubin (DBL), prolonged prothrombin time (PT) or international normalized ratio (INR) (INR > 1.5), hepatic encephalopathy, or ascites caused by impaired hepatic function [35].

### 2.5. Common terminology criteria for adverse events (CTCAE)

In most published oncology studies, including those using ICIs, liver test abnormalities are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) versions 3 to 5, which categorize serum ALT and AST elevations as grade 1 (> ULN-3x ULN), grade 2 (> 3–5x ULN), grade 3 (> 5–20x ULN), and grade 4 (> 20x ULN) [41]. Because of the prevalent use of the CTCAE grading system, only a minority of clinical trials using ICIs provide detailed data on subgroups of ALT or AST elevations such as > 8x ULN or > 10x ULN. The CTCAE assigns each grade a severity degree: grade 1, mild; grade 2, moderate; grade 3, severe, and grade 4, life threatening. However, there are few published data to support an association between the magnitude of ALT or AST elevation and the clinical outcome of the liver injury [42,43]. As a result, most authorities avoid the use of the severity terminology for the various CTCAE stages [42,44]. For practical purposes, the IQ DILI IWG agreed to use the CTCAE grading scale (grades 1 through 5) in this consensus paper, to align with data provided in many published clinical studies of ICIs.

### 2.6. Consensus and recommendations

1. The preferred term for cases of liver injury caused by ICIs is "immune-mediated liver injury caused by immune checkpoint inhibitors" (ILICI).
2. For patients with mild asymptomatic elevations of serum ALT or AST (< 3x ULN) the terms "ALT elevation" or "AST elevation" are preferred to "ILICI".
3. Until a larger histological database of patients with suspected ILICI is available, the term "hepatitis" should be reserved for patients who have histological findings consistent with hepatitis.
4. In established ILICI with predominantly elevated serum ALP and GGT, the preferred term is "cholestatic ILICI". Histologic terms such as "cholangitis" should be reserved for patients who have supportive histological findings or results of other reliable diagnostic tests.
5. In patients with ILICI, the terms "liver dysfunction" and "liver failure" should be reserved for those with evidence of decreased liver function (e.g., prolonged PT/INR or elevated serum levels of DBL or TBL) or evidence of acute decompensation (e.g., hepatic encephalopathy, ascites).
6. It is recommended to avoid the use of clinical severity terms (e.g., mild, moderate, severe, as suggested by CTCAE grading) based solely on elevated ALT or AST levels in patients with ILICI.

## 3. ILICI incidence in clinical trials

The reported incidence of ILICI varies among the different agents as well as across trials and indications. Furthermore, reported rates differ considerably due to differences in terminology and variations in ALT or AST cutoff values used to define ILICI. In most large clinical trials using a single ICI, serum ALT elevations > ULN occurred in 3–15% of patients during ICI treatment [16,45–54]. A few studies reported a higher incidence; however, these data are difficult to interpret because a substantial percentage of mild ALT changes (< 3x ULN) were transient or not related to exposure to the study drug [18,55,56]. Grade 3 ALT elevations (ALT > 5–20x ULN) occurred in 0–3% of the patients treated with a single ICI, while grade 4 ALT elevations (ALT > 20x ULN) occurred in 0–0.5% of the cases [46,49,51–53,57–62]. These incidence rates are consistent with retrospective studies from the US and France which showed grade 3–4 ILICI incidence of 1.7% and 3% in 5762 and 536 patients, respectively [33,34]. The incidence of ILICI associated with ipilimumab monotherapy, ranging between 3 and 9%, was on average higher than that of other ICIs [2,52,53,55,63,64].

While well documented in the post-marketing setting, concomitant elevation of serum ALT > 3x ULN and total bilirubin (TBL) > 2x or > 3x ULN has been infrequent in clinical trials using ICIs [12,13,33,65]. Acute liver failure due to ICIs was also rarely reported in clinical trials, and mostly observed post-marketing [12,13,15,33]. A recent meta-analysis reported 8 fatal ILICI cases out of 19,127 treated patients (0.042%) [66]. In a few studies the incidence of ILICI appeared to be dose dependent [3,67–69].

To date, published data are insufficient to estimate the true incidence of cholestatic ILICI, defined as an R value (serum ALT/ULN divided by serum ALP/ULN) < 2, measured near the time of onset of liver injury [37]. Acute cholestatic ILICI has been reported infrequently in clinical trials, however, in post marketing reports cholestatic or mixed liver injury was reported in up to 20–30% of affected patients [23–26]. In retrospective post marketing studies, patients with

cholestatic injury were uncommon, or were not included in the analysis [26,33,34]. In one retrospective analysis, of 20 patients who were adjudicated as definite or highly likely to be drug-related, 40% had an acute hepatocellular pattern (R value > 5), 25% had a mixed pattern (R value 2–5), and 35% had a cholestatic pattern at the onset of liver injury [26]. However, since ALP elevations are often the result of tumor-related causes, it is difficult to determine the true incidence of cholestatic and mixed ILICI.

### 3.1. Combination anti-neoplastic regimens in clinical trials

Accumulated evidence suggests that combinations of two or more ICIs or of one ICI with other chemotherapeutics with hepatotoxic potential may increase the incidence of ILICI [6,8,17,33,54,70,71]. Animal studies have shown that concomitant checkpoint inhibition increases the risk of DILI due to drugs with a known DILI risk, such as amodiaquine [72]. In clinical trials combinations of two ICIs (e.g., ipilimumab and nivolumab) were associated with higher incidence of serum ALT elevations (11–18% grade ≥3) compared to individual administration as monotherapy (0–3%) [17,54,73]. An increased incidence of ALT elevations was also observed using a combination of vemurafenib (BRAF inhibitor) and ipilimumab. In a phase I study, 4 of 6 patients had grade 3 ALT or AST elevations in one cohort, and 3 of 4 patients had grade 2 or 3 ALT or AST elevations in a second cohort, which led to an early termination of the study [68]. It should be noted that the liver adverse events were asymptomatic and were reversible upon discontinuation of the study drug and the administration of corticosteroids in a few instances. In a prospective clinical trial comparing ipilimumab plus dacarbazine to dacarbazine plus placebo in patients with metastatic melanoma, grade 3–4 ALT elevations occurred in 20.7% of the patients using the ipilimumab-dacarbazine combination compared to 0.8% of patients on dacarbazine alone. Grade 4 ALT elevations occurred in 5.2% of the patients on ipilimumab-dacarbazine versus 0% of the patients on dacarbazine only [70]. Furthermore, the rate of grade 3–4 ALT elevation was higher with the combination of ipilimumab-dacarbazine compared to that reported for ipilimumab alone (20.7% vs. 8% respectively) [70,74,75]. The reason for the apparent increase in the rate of liver injury associated with combination ipilimumab-dacarbazine remains unclear. It has been postulated that the increase in liver injury rates may be related to lowering of the immune threshold to dacarbazine-related DILI, induced by ipilimumab.

A higher incidence of ILICI with the combination of two ICIs has also been reported in the clinical practice setting [33,34]. In a recent retrospective study of 5762 patients, combination therapy of two ICIs was found to be associated with an ILICI rate (grade 3–4 ALT elevation) of 9.2% compared to 1.7% with monotherapy [33].

Despite a paucity of clinical evidence, it is believed, that patients who have received previous ICI treatment are at an increased risk of DILI from a subsequent drug with hepatotoxic potential (whether an ICI or not), compared to patients who were not previously exposed to ICIs. There are a few case reports to support this notion, but it largely remains untested [71].

### 3.2. Special populations

**Pre-existing chronic liver disease.** Hepatic safety data in patients with chronic liver disease such as chronic hepatitis B or C, alcohol-related liver disease or nonalcoholic steatohepatitis (NASH) remain scarce, because most initial studies using ICIs excluded such patients [76]. However, reports of ICI treatment in patients with chronic hepatitis B or C are increasing, mainly due to the use of ICIs for the treatment of hepatocellular carcinoma (HCC) [32,77–79]. Based on recent studies, both nivolumab and pembrolizumab have gained accelerated approval status from FDA for the treatment of HCC [62,79–81]. A few authors have suggested that ICIs may promote worsening of underlying liver disease through various speculative mechanisms; however, evidence for this remains insufficient [2,18,77]. In chimpanzees with naturally occurring hepatitis B virus (HBV), dosing with pembrolizumab was associated with serum AT elevations in 2 out of 4 animals. These AT elevations were not completely resolved at the end of a 4-week off-dosing period [62,82]. The underlying mechanism of this finding is unclear. In a woodchuck model of chronic hepatitis virus (which closely resembles human chronic HBV infection), the addition of anti-PD-L1 antibody to an anti-viral regimen significantly enhanced the suppression of hepatitis virus, leading to complete viral clearance in some cases [83]. Similarly, when 3 chimpanzees with persistent hepatitis C virus (HCV) infection were treated with multiple doses of anti-PD-1 antibody, there was a significant reduction in viral load in one animal in the absence of apparent hepatic injury [84]. In cirrhotic patients with HCV infection who were treated for HCC with tremelimumab, the frequency of grade 3–4 ALT elevation (25%) was notably higher than in HCC patients without HCV (3%) [60,85]. However, some ALT elevations were likely caused by the underlying HCV rather than by tremelimumab. Interestingly, tremelimumab treatment was associated with a progressive decrease in HCV viral load (HCV RNA) in most patients followed for at least 3 months [85]. In other reports of smaller sample size, ILICI was either not observed or was uncommon (grade 3 ALT elevation in one case) in patients with either HBV or HCV, including those with detectable viral load treated with ipilimumab, pembrolizumab, nivolumab or atezolizumab. In addition, none of the patients had significant changes in HCV viral load [77,78]. Other case reports have shown no effect on HCV RNA during ICIs treatment with or without concomitant direct acting antiviral therapy for HCV [86]. Recently, the American Society of Clinical Oncology (ASCO) and the Friends of Cancer Research advocated that clinical trial eligibility criteria for ICIs be expanded, to reflect 'real-world' treatment populations (including chronic hepatitis B or C), which may aid in better characterization of the safety of ICIs in patient populations with pre-existing chronic liver disease [2,87,88].

**Liver transplant recipients.** Hepatic safety of ICIs in liver transplant recipients is controversial, because of conflicting reports regarding the risk of ILICI and graft rejection in this patient population [78,89,90]. The increasing number of published reports of allograft rejection has raised questions about publication bias [32]. However, reports of severe rejection resulting in death emphasize the need for a cautious approach to treatment and close monitoring in liver transplant recipients treated with ICIs [78,91].

### 3.3. Consensus

7. The incidence of ILICI varies among different ICIs and clinical trials. Most publications reported the incidence of grade 3 serum ALT elevations (> 5–20x ULN) to be 1–2.5% of the patients treated with a single ICI. Grade 4 ALT elevations (> 20x ULN) occurred in 0–0.5% of cases. Generally, the frequency of ALT elevations was higher with the CTLA-4 inhibitor, ipilimumab, than with PD-1 and PD-L1 inhibitors.
8. Grade 3–4 serum TBL elevation (> 3x ULN) with concurrent ALT elevation was reported in less than 0.1% in patients treated with a single ICI.
9. Liver failure attributed to ICIs has been reported rarely.
10. Generally, combination therapy with two or more ICIs or an ICI with another chemotherapeutic drug with a known DILI risk, has been associated with a higher rate of grade 3–4 ALT elevations. The incidence of grade 3–4 ALT elevations varies among specific drug combinations.
11. Data from animal studies suggest that concurrent checkpoint inhibition may increase the risk of DILI caused by other drugs with a known risk of DILI.
12. Limited data exist regarding the risk of ILICI in patients with chronic liver disease including chronic hepatitis B or C, alcoholic liver disease or NASH.

13. Cases of cholestatic ILICI have been reported; however, the incidence of this type of liver injury is not clearly defined.
14. The incidence of ILICI or graft rejection in liver transplant recipients is not yet established, but an increased risk seems likely, based upon published reports.

## 4. Hepatic inclusion and exclusion criteria in ICI clinical trials

In general, the purpose of hepatic inclusion and exclusion criteria is to minimize potential DILI risk, prevent drug accumulation due to diminished hepatic excretion/metabolism, and decrease confusion between potential DILI and progression of preexisting liver disease. Hepatic inclusion and exclusion criteria have varied considerably among ICI trials (Suppl Table S1). Exclusion criteria for serum ATs have ranged between > 1.5x ULN and > 3x ULN in patients without hepatic metastases [45,56,61,70,92–94]. In patients with hepatic metastases most studies have allowed inclusion of patients with serum ALT or AST levels of up to 5x ULN [50,56,94–96]. Exclusion criteria for serum TBL typically have ranged from > 1.0x ULN to > 2.5x ULN, with the exception of patients with Gilbert's syndrome who were enrolled with higher serum TBL, usually < 3.0 mg/dL [45,50,56,61,92,94–100]. Of note, the diagnosis of Gilbert's syndrome in a patient with elevated TBL, is typically confirmed by calculating the amount of DBL, which should be less than 30% of the TBL, in the absence of hemolysis [101,102]. In a few ICI studies, DBL > ULN has been added as a separate exclusion criterion [50]. To date, most ICI clinical trials in patients with HCC have excluded patients with baseline serum ALT or AST > 5x ULN, or TBL > 2.5x ULN [85]. No consistent differences exist between the exclusion criteria used in particular studies, the types of cancer, or the specific ICIs being administered. Moreover, no systematic trials have been performed to compare and assess different thresholds of serum ALT, AST, and TBL for enrollment criteria. Thus, no data exist to favor one set of criteria over another.

Most studies of ICIs for patients with cirrhosis and HCC have excluded patients with advanced liver disease defined by a Child Turcotte Pugh (CTP) score of > 7 (CTP class C or class B with a score of 8–9) [79–81]. Very few studies allowed inclusion of CTP class B with a score of 8–9, however CTP class C (score 10–15) were generally excluded [85]. This reduces the likelihood of confusing ILICI (or other types of DILI) for development of a complication of cirrhosis such as hepatic decompensation or portal vein thrombosis, which are more likely in patients with advanced liver disease.

While initial clinical trials of ICIs excluded patients with chronic liver disease due to hepatitis B or C (Suppl Table S1), a growing body of evidence indicates that such patients may not exhibit a significantly increased risk of ILICI or reactivation of hepatitis B or C [77–79,85,103,104]. Indeed, the increased use of ICIs for treatment of HCC in patients with chronic HBV or HCV infection (major risk factors for the development of HCC) have shown promising results [79,81,104]. In most such studies, patients with HBV infection were required to be on suppressive nucleos(t)ide analogue therapy with a viral load (HBV DNA) < 100 IU/mL during screening. Direct acting antiviral therapy to achieve a sustained virologic response was not a prerequisite for ICI treatment of patients with HCV infection [79,85]. Interestingly, antiviral T-cell activities regulated by the PD-1/PD-L1 pathway are known to be decreased in chronic viral hepatitis (HBV, HCV), and in vitro studies suggest that blocking this pathway may reduce viremia [105,106]. This is in accordance with evidence of a decreased HCV viral load (HCV RNA) observed in HCC patients treated with the CTLA-4 inhibitor tremelimumab [85].

The question of whether patients with preexisting autoimmune hepatitis (AIH) can be enrolled in clinical trials using ICIs, is still unresolved. Although prospective data are scarce, some evidence suggests that patients with a history of autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroiditis, psoriasis, and inflammatory bowel disease, are at a higher risk of irAEs and flares of their preexisting autoimmune disorders while on ICIs [107–109]. However, these events were often mild, manageable, and did not typically necessitate discontinuation of ICI therapy, while a significant proportion of patients achieved clinical anti-cancer responses. Nevertheless, such events may be severe on occasion [109]. At present, there are no published data documenting flares of idiopathic AIH. Extrapolation from the data on other autoimmune diseases suggests that in some instances ICIs can be administered relatively safely to patients with idiopathic AIH with close monitoring of hepatic biochemical tests [107–109]. A liver biopsy prior to initiation of treatment may help in the assessment of disease activity and severity [110].

### 4.1. Consensus and recommendations

15. To allow accurate evaluation of ILICI risk as well as DILI risk due to concomitant medications, it is recommended that patients with serum ALT > 3x ULN be excluded from ICI clinical trials unless HCC metastatic disease is present. In the presence of hepatic primary or metastatic disease it is recommended to exclude patients with serum ALT > 5x ULN.
16. Since elevated serum ALP is common in patients with malignancy, using serum ALP levels as an exclusion criterion in otherwise eligible study participants is generally not recommended.
17. It is recommended that patients with a baseline elevation of TBL > 1.5x ULN be excluded. Patients with a TBL elevation due to Gilbert's syndrome can be included in clinical trials using ICIs, provided that the serum DBL is less than 30% of the TBL, in the absence of hemolysis.
18. Patients with chronic hepatitis B can be enrolled in clinical trials of ICIs, if they have baseline serum HBV DNA < 100 IU/mL and normal or near normal serum ALT (< 1.5x ULN), while on treatment with anti-HBV therapy using an approved nucleos(t)ide analogue.
19. Patients with acute hepatitis A, B, C, D or E, reactivated hepatitis B, or active delta hepatitis should be excluded until their clinical status and liver disease stabilize.
20. Patients with a history of chronic hepatitis C or positive anti HCV antibody who have undetectable serum HCV RNA at baseline (following anti-HCV treatment or after spontaneous clearance) may be enrolled in clinical trials of ICIs with routine monitoring of ALT, AST and TBL according to the protocol schedule.
21. Patients with chronic hepatitis C and *detectable* serum HCV RNA may be enrolled in clinical trials with ICIs. There are no consistent recommendations regarding anti-HCV treatment in these patients. It is recommended to obtain serum HCV RNA whenever serum ALT increases to > 3x ULN.
22. There are limited data regarding the safety and efficacy of ICI therapy in patients with idiopathic AIH. Despite the absence of published reports, a flare of idiopathic AIH remains a theoretical risk of ICI therapy.
23. Patients with idiopathic AIH may be enrolled in clinical trials with ICIs if their disease is stable, well-controlled with immunosuppressive therapy, and with normal or near normal liver tests. A liver biopsy prior to initiation of ICI treatment can help in assessing the activity and severity of the AIH.
24. Patients with idiopathic AIH, whose liver disease is well controlled with immunosuppressive therapy should continue receiving their therapy during ICI treatment. Investigators should be mindful of the potential risk of a flare of idiopathic AIH and should follow these patients closely.
25. There are insufficient published data to recommend inclusion or exclusion of liver transplant recipients in clinical trials with ICIs.

## 5. Hepatic monitoring and ILICI detection

Close monitoring of clinical status and liver test results is critically

important for early detection, risk assessment, and management of ILICI during drug development for ICIs [2,7,8,21,35]. Since ILICI most commonly presents with asymptomatic elevations of serum ATs, most cases have been detected through monitoring of hepatic biochemical tests. Serum ALP typically remains within the normal range in ILICI, but mild elevations, usually < 2x ULN, may occur. In a minority of the patients, ILICI presented with hepatic symptoms such as general weakness, fatigue, abdominal discomfort, nausea, vomiting, or fever [15]. Generally, patients with symptomatic ILICI tended to have higher serum ATs, which may be > 20x ULN and occasionally > 40x ULN [23]. The typical time to onset (latency) ranged from 2 to 24 weeks (median 4–16 weeks) from initiation of ICI treatment, although several well documented ILICI cases occurred after longer treatment duration (e.g., 48 weeks) (Suppl Table S2) [7,11,33,63,81,111–114].

Most clinical trials of ICIs require serial assessments for signs and symptoms of liver injury, and hepatic biochemical tests (serum ALT, AST, ALP, and TBL) every 2–3 weeks during the first 2–3 months, and every 3–4 weeks thereafter [46,60,100,115]. Typically, assessments are made before the subsequent cycle of ICI treatment, ending 1–3 months after completion or discontinuation of treatment. This is in keeping with general recommendations made in the US FDA's guidance on the premarketing evaluation of DILI [35] as well as clinical practice guidelines from ASCO, the European Society for Medical Oncology (ESMO), Society for Immunotherapy of Cancer (SITC), and the National Comprehensive Cancer Network (NCCN) [7–9,21].

In general, when assessing a case of suspected DILI in patients without underlying liver abnormalities, the magnitude of change in hepatic biochemical tests is determined in comparison to the ULN [35]. In patients with preexisting elevations of liver tests it has been recommended to assess the change in comparison to the patient's baseline values [35,41,116]. Therefore, it is crucial to establish a baseline for reference, prior to ICI initiation. Since serum ALT levels in some oncology patients can fluctuate even over short periods of time (especially in the presence of hepatic tumors or metastases and with certain

**Table 1**
Recommended management of treatment emergent abnormal hepatic biochemical tests in clinical trials with ICIs (patients with normal or near-normal baseline ALT, AST[a] [ < 1.5x ULN]).

| CTCAE grade of ALT/AST elevation | Serum ALT or AST | Serum TBL[b] | ICI treatment adjustment and additional therapy | Monitoring and evaluation |
|---|---|---|---|---|
| Grade 1 | ALT or AST > ULN –3x ULN | Normal | Continue treatment | Repeat blood tests[c] within 1–2 weeks. |
| Grade2 | ALT or AST > 3–5x ULN | **Patients with Gilbert's synd:** No change in baseline TBL<br>Normal | WithholdICI treatment.<br>If rising ALT/AST when re-checked, start oral prednisone/prednisolone 1 mg/kg/d[f] | Repeat blood tests[d] within 2–5 days. Initiate close monitoring[e] and evaluation (Table 3). |
| Grade 2 | ALT or AST > 3–5x ULN | Patients **with Gilbert's synd:** No change in baseline TBL<br>TBL ≥2x ULN | Discontinue ICI treatment.<br>Start I.V. (methyl) prednisolone 1–2 mg/kg/d[f] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| Grade 3 | ALT or AST > 5–10x ULN | **Patients with** Gilbert's **synd:** Doubling of direct bilirubin<br>Normal | Withhold ICI treatment.<br>Start oral prednisone/prednisolone 1–2 mg/kg/d[f] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| Grade 3 | ALT or AST > 5–10x ULN | **Patients with Gilbert's synd:** No change in baseline TBL<br>TBL ≥2x ULN | Discontinue ICI treatment.<br>Start oral prednisone/prednisolone 1–2 mg/kg/d[f] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| Grade 3 | ALT or AST > 10–20x ULN | **Patients with Gilbert's synd:** Doubling of direct bilirubin<br>Normal or abnormal | Discontinue ICI treatment.<br>Start I.V. (methyl)prednisolone 1–2 mg/kg/d[g] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| Grade 4 | ALT or AST > 20x ULN | Normal or abnormal | Discontinue ICI treatment.<br>Start I.V. (methyl) prednisolone 2 mg/kg/d[g] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |

Abbreviation used: ALP, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; DBL, direct bilirubin; GGT, gamma glutamyl transferase; ICI, immune checkpoint inhibitors; INR, International Normalized Ratio; MMF, mycophenolate mofetil; TBL, total bilirubin; ULN, upper limit of normal.

[a] Use of serum ALT is preferred over AST due to its higher hepatic specificity. ALP is not included in this table as isolated ALP elevation is often related to the underlying malignancy and uncommonly related to ILICI. Furthermore, there are limited published data regarding management of ILICI in patients who develop isolated ALP elevation during ICI treatment.

[b] Measurement of total and conjugated (or direct) bilirubin is recommended to help identify patients with indirect hyperbilirubinemia due to Gilbert's syndrome or hemolysis versus liver injury.

[c] Recommended blood tests include ALT, AST, ALP, GGT, TBL.

[d] Recommended blood tests include: ALT, AST, ALP, GGT, TBL, DBL, CK, INR.

[e] Initial monitoring should be 2–3 times a week. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until levels return to Grade 1, regardless of whether or not the ICI had been discontinued.

[f] **Oral prednisone/prednisolone:** if hepatic biochemical tests worsen on oral prednisone/prednisolone, change to I.V. (methyl)prednisolone. Once hepatic biochemical tests return to Grade 1, corticosteroids can be weaned over 2–4 weeks. ICI treatment may be resumed with close monitoring, once prednisone/prednisolo[f]e dose ≤10 mg/day.

[g] **I.V. (methyl)prednisolone:** if worsening continues on I.V. (methyl)prednisolone, consider adding MMF 500–1000 mg twice daily. See additional options in text. Once hepatic biochemical tests return to Grade 1, corticosteroids can be weaned over 4 weeks. ICI treatment may be resumed with close monitoring, once prednisone/prednisolone dose ≤10 mg/day.

concomitant anti-neoplastic agents), a single measurement on a given day may not be representative of a patient's true baseline. Thus, it has been suggested to obtain at least two serum ALT measurements at least one week apart prior to treatment initiation and to use the average of the two values as the baseline value [37,116]. These two measurements can be performed at the "screening visit" (typically visit 1) and the "baseline visit" just prior to initiation of the study drug (typically visit 2 or 3). Most clinical trials of ICIs require at least 2 baseline measurements of serum ALT, AST, ALP and TBL to provide reference values for assessing any on treatment changes. If the two ALT values differ by > 50%, and the higher value is > 2x ULN, it has been recommended to consider performing a third test to determine the direction of the change, and to consider evaluation for cause prior to enrollment [116,117].

In keeping with the FDA's guidance on DILI and clinical guidelines on ILICI, it has been strongly recommended to initiate close observation immediately upon detection and confirmation of early signs of possible ILICI, and not to wait until the next scheduled visit or monitoring interval. Serum ALT levels greater than 3x ULN (in patients with normal or near normal baseline ALT) or greater than 2x baseline value (in patients with baseline ALT ≥1.5x ULN) have been proposed for initiation of close observation [7–9,21,35]. Close observation usually includes repeat testing of ALT, AST, TBL, DBL, ALP and GGT, followed by serial monitoring of these tests (initially, 2–3 times a week) (Tables 1 and 2). Once an abnormality is confirmed, a comprehensive assessment should be undertaken to determine the likelihood of ILICI and exclude alternative causes of liver injury [7–9,21,35,37,116,117]. Initial monitoring should be done at a frequency of 2–3 times weekly, based on the clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be reduced to once every 1–2 weeks, if the clinical condition and lab results stabilize [7–9,21,35].

### 5.1. Consensus and recommendations

26. ILICI most commonly presents as asymptomatic serum ALT and AST elevation with ALP levels in the normal or moderately elevated range, a pattern consistent with hepatocellular or mixed injury.
27. Reference-baseline values of serum ALT may need to be established based on a calculation of the average of two consecutive ALT levels performed at least 1 week apart prior to initial dosing (preferably during the screening and baseline visits). If the two ALT values differ by > 50%, and the higher value is > 2x ULN, it is

**Table 2**
Recommended management of treatment emergent abnormal hepatic biochemical tests in clinical trials with ICIs (patients with abnormal baselineALT, AST[a] [≥1.5x ULN]).

| Serum ALT or AST | Serum TBL[b] | ICI treatment adjustment and additional therapy | Monitoring and evaluation |
|---|---|---|---|
| ALT or AST > BLV –2x BLV | Normal | Continue treatment | Repeat blood tests[c] within 1–2 weeks. |
| ALT or AST > 2–3x BLV | **Patients with Gilbert's synd:** No change in baseline TBL<br>Normal | Withhold ICI treatment.<br>If rising ALT/AST when re-checked, start oral prednisone/prednisolone 1 mg/kg[f] | Repeat blood tests[d] within 2–5 days. Initiate close monitoring[e] and evaluation (Table 3). |
| ALT or AST > 2–3x BLV | **Patients with Gilbert's synd:** No change in baseline TBL<br>TBL ≥2x ULN | Discontinue ICI treatment.<br>Start I.V. (methyl) prednisolone 1–2 mg/kg[f] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| ALT or AST > 3– < 5x BLV | **Patients with Gilbert's synd:** Doubling of direct bilirubin<br>Normal | Withhold ICI treatment.<br>Start oral prednisone/prednisolone 1–2 mg/kg[f] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| ALT or AST > 3– < 5x BLV | **Patients with Gilbert's synd:** No change in baseline TBL<br>TBL ≥2x ULN | Discontinue ICI treatment.<br>Start oral prednisone/prednisolone 1–2 mg/kg[f] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |
| ALT or AST > 5x BLV | **Patients with Gilbert's synd:** Doubling of direct bilirubin<br>Normal or abnormal | Discontinue ICI treatment.<br>Start I.V. (methyl) prednisolone 1–2 mg/kg[g] | Repeat blood tests[d] within 2–3 days. Initiate close monitoring[e] and evaluation (Table 3). |

ALP, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartate aminotransferase; BLV, baseline value; Dir Bil, direct bilirubin; ICI, immune checkpoint inhibitors; INR, International Normalized Ratio; MMF, mycophenolate mofetil; TBL, total bilirubin; ULN, upper limit of normal.

[a] Use of serum ALT is preferred over AST due to its higher hepatic specificity. ALP is not included in this table as isolated ALP elevation is often related to the underlying malignancy and less commonly related to ILICI. Furthermore, there are limited published data regarding management of ILICI in patients who develop isolated ALP elevation during ICI treatment.

[b] Measurement of total and conjugated (or direct) bilirubin is recommended to help identify patients with indirect hyperbilirubinemia due to Gilbert's syndrome or hemolysis versus liver injury.

[c] Recommended blood tests include ALT, AST, ALP, GGT, TBL.

[d] Recommended blood tests include: ALT, AST, ALP, GGT, TBL, Dir Bil, CK, INR.

[e] Initial monitoring should be 2–3 times a week. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until levels return to Grade 1, regardless of whether or not the ICI had been discontinued.

[f] **Oral prednisone/prednisolone:** if hepatic biochemical tests worsen on oral prednisone/prednisolone, change to I.V. (methyl)prednisolone. Once hepatic biochemical tests return to Grade 1, corticosterids can be weaned over 2–4 weeks. ICI treatment may be resumd with close monitoring, once prednisone/prednisolone dose ≤10 mg/day.

[g] **I.V. (methyl)prednisolone:** if worsening continues on I.V. (methyl)prednisolone, consider adding MMF 500–1000 mg twice daily. See additional options in text. Once hepatic biochemical tests return to Grade 1, corticosteroids can be weaned over 4 weeks. ICI treatment may be resumed with close monitoring, once prednisone/prednisolone dose ≤10 mg/day.

recommended to perform a third test to determine the direction of the change, and to consider evaluation for the cause.

28. In patients with a normal or near normal baseline serum ALT (< 1.5x ULN), a confirmed ALT elevation of ≥3x ULN, regardless of hepatic symptoms or TBL values, is a reasonable threshold to initiate close observation and more frequent monitoring (Table 1)
29. In patients with an elevated baseline serum ALT (≥1.5xULN), an ALT elevation of > 2x baseline, even in the absence of hepatic symptoms or elevated TBL, is a reasonable threshold to initiate close observation and monitoring (Table 2).
30. In patients meeting the criteria for possible ILICI, an assessment for hepatic signs or symptoms and liver tests (including ALT, AST, ALP, TBL) should be repeated within 2–3 days and at least weekly thereafter until a return to pre-event baseline values occurs. The specific interval between the tests should be determined based on the patient's clinical condition and the course of change in hepatic biochemical tests.

## 6. Special considerations for causality assessment of suspected ILICI

Like other DILI types, causality assessment in patients with suspected ILICI is challenging and largely dependent on the exclusion of other possible causes of liver injury [118]. A comprehensive discussion of principles and methods of causality assessment is beyond the scope of this publication. The following section addresses specific considerations pertinent to ILICI.

Abnormal liver tests related to ILICI should be differentiated from those that may occur due to other causes of liver injury associated with the underlying malignancy or concomitant medications. Patients with malignant tumors may have elevated serum levels of ALT, AST or ALP, due to a variety of causes including hepatic metastases, biliary obstruction, hepatic vein thrombosis, congestive heart failure, systemic infections, metastatic spread to bone and other organs [26,38,119]. They may also develop DILI due to drugs other than ICIs, as well as from herbal/dietary supplements. The frequency of serum ALP > 1x ULN ranges between 37.2% in patients without detectable hepatic metastases and as high as 67% in patients with hepatic metastases [119]. The pattern of liver injury in ILICI is typically hepatocellular, or (less often)

**Table 3**
Recommended evaluation of patients with treatment-emergent grade 2–4 ALTelevation during a clinical trial with ICIs[a].

| Recommended evaluation | Competing causes of abnormal liver tests |
|---|---|
| 1st Line Testing | |
| Thorough history of symptoms, co-existing medical conditions, concomitant medications, dietary and nutritional supplements, excessive exercise or muscle injury, alcohol consumption, illicit substances. | Systemic infection/sepsis; ischemic/congestive hepatic injury; gallstone disease; alcoholic liver disease; muscle injury/rhabdomyolysis; acetaminophen toxicity; DILI due to another drug, herbal or dietary supplement. |
| Serum CK | Muscle injury/rhabdomyolysis[c] |
| Anti-HAV (IgM) | Acute HAV infection |
| HBsAg | Acute hepatitis B; Exacerbation of chronic hepatitis B |
| Anti-HBc IgG, IgM, HBV DNA | |
| Anti-HCV | Acute hepatitis C; |
| HCV RNA (PCR) | Exacerbation of chronic hepatitis C[b] |
| Anti-HEV (IgG, IgM); HEV RNA[d] | Acute hepatitis E |
| ANA, ASMA | Autoimmune hepatitis[e] |
| Quantitative immunoglobulins (IgG, IgM, IgA) | |
| Hepatobiliary imaging (ultrasonography, CT scan, MRI, MRCP)[f] | Biliary obstruction; pancreatitis; gallstones; portal-vein/hepatic vein thrombosis; hepatic metastasis |
| **2nd Line Testing** | |
| Serological tests for EBV, CMV, HSV. | Hepatic injury caused by CMV, EBV, HSV |
| May need to obtain acute and convalescent serological tests; | |
| EBV-DNA, CMV-DNA, HSV-DNA by PCR. liver biopsy needed to confirm HSV | Hepatic injury caused by CMV, EBV, HSV |
| Additional **Tests**[g] | |
| Anti-LKM-1 | Autoimmune hepatitis |
| Serum EtOH | Alcohol related liver disease |
| Urinary ethyl-glucuronide and ethyl-sulfate[h], Serum phosphatidylethanol[i] | |
| Serum acetaminophen level; Acetaminophen protein adducts | Acetaminophen toxicity |
| Review of blood pressure, pulse, electrocardiogram, echocardiogram, cardiology consult | Ischemic or congestive hepatic injury |
| Urine toxicology screen | Hepatotoxicity due to cocaine, amphetamines, opiates and other illicit substances |
| Anti-HDV | Hepatitis D |
| Blood or urine cultures | Systemic infection, sepsis |
| Blood ceruloplasmin, serum copper | Wilson's disease |
| Slit lamp eye examination for Kayser-Fleischer rings, genetic testing | |

Abbreviations used: CMV, Cytomegalovirus; CK, creatine kinase; DILI, drug induced liver injury; EBV, Epstein Bar Virus; HBV, hepatitis B virus, HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV; Herpes Simplex Virus; LKM-1, liver kidney microsomal type 1.

[a] Extent and type of work-up may vary by patient's history, severity of liver injury, underlying disease, and geography.
[b] Acute hepatitis C may be anti-HCV negative but HCV RNA positive.
[c] Serum AST typically (although not always) is higher than ALT.
[d] If anti-HEV IgM positive, consider confirmation with HEV RNA by nested PCR.
[e] A liver biopsy is needed to confirm a diagnosis of AIH.
[f] If cholestatic injury, MRCP may be recommended.
[g] Based on medical history and clinical judgment.
[h] Alcohol consumption in past 3–5 days.
[i] Alcohol consumption in past 3 weeks.

mixed, i.e., predominantly ALT and AST elevation, with a R value > 5 or 2–5, and therefore usually easy to differentiate from hepatic metastasis, which is typically cholestatic. Nevertheless, ILICI may infrequently also present as cholestatic injury (R value < 2), which can cause a diagnostic dilemma [23,24,26].

A comprehensive causality assessment is required in all patients who meet criteria for suspected ILICI during a clinical trial (Table 3). A recent retrospective study found that fewer than 30% of patients who met criteria for liver injury (serum ALT ≥5x ULN/baseline, ALP ≥2x ULN/baseline, TBL ≥2.5 mg/dL or 2x baseline) had ILICI based on adjudication by expert opinion [26]. Most clinical trials have required the following assessment for patients with suspected ILICI: (1) a thorough history of symptoms, concomitant medications (including recent acetaminophen overdose), use of herbal/dietary and nutritional supplements, and recent alcohol consumption; (2) repeat testing of ALT, AST, ALP, TBL, DBL, and albumin, followed by close monitoring of these biochemical tests; (3) testing of serum for viral hepatitis including hepatitis A, B, C, E, and testing for HDV in patients who are infected with HBV; (4) serological tests for autoimmune hepatitis, including anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-kidney microsomal antibodies, and quantitative immunoglobulins; (5) hepatobiliary imaging to rule out other causes of liver injury such as cholecystitis, choledocholithiasis, biliary obstruction, and hepatic vein thrombosis. If results of the initial testing do not reveal an alternative cause, additional tests may be considered, including tests for cytomegalovirus (CMV), Epstein Barr virus (EBV), herpes simplex virus (HSV), additional imaging, and/or a liver biopsy. A consultation with a clinician knowledgeable in DILI or a hepatologist has been recommended to assess complex cases. This approach is consistent with most published clinical guidelines pertaining to post marketing assessment of patients with suspected ILICI [7–9,21]. To enable an analysis of hepatotoxic risk, it is important to systematically collect and document the results of these tests in the patient's case report forms [35].

In patients receiving a combination of an ICI and a non-ICI drug that may have a hepatotoxic liability, differentiating between ILICI and DILI due to the concomitant non-ICI drug can be especially challenging. Moreover, as described above, certain combined treatments have shown more liver toxicity than each component alone. Concurrent irAEs (e.g., skin manifestations, colitis, thyroiditis, pneumonitis), which are relatively common in patients with ILICI, occurring in about 30–47%, may indicate that the ICI is a more likely cause of liver injury than the non-ICI drug, but other factors (e.g., temporal relationship, dechallenge, rechallenge, known DILI phenotype of each drug) must be considered [15,18,33,34,71].

In some cases, it may be difficult to differentiate between ILICI and idiopathic AIH. One important distinguishing feature is that in contrast to a high recurrence rate of classical idiopathic AIH after discontinuation of corticosteroid treatment, in ILICI, corticosteroid treatment typically leads to a long-lasting resolution of liver test abnormalities after ICI discontinuation [18,33]. Recurrence of ILICI after steroid withdrawal has been reported in only 14% of patients [33]. Furthermore, in contrast to idiopathic AIH, in which 90% of patients have high titers of serum autoantibodies, including ANA, anti-double stranded DNA antibody, and ASMA, most ILICI cases are marked by the absence of elevated titers of these antibodies [2,33,34,120,121]. Liver histology may also be helpful in differentiating between ILICI and idiopathic AIH (see below).

Imaging studies do not show specific findings associated with ILICI and may show either normal appearance or mild periportal lymphadenopathy, periportal edema or hepatomegaly in severe cases. However, imaging studies may be helpful in ruling out other causes of acute increase in liver tests, such as worsening of hepatic metastasis, biliary obstruction, and hepatic vein or portal vein thrombosis [13,23].

According to most experts, liver biopsy is usually not necessary for the routine diagnosis or management of ILICI but may be helpful in patients who fail to respond to conventional therapy, or in whom the diagnosis is questionable due to atypical presentation or unusual clinical course [7–9,21,122]. In such cases, liver histology can provide important and useful information on the pattern of injury and its severity and may help identify causes other than ILICI [23,25,31,34,122–124]. In most patients with ILICI, liver histopathology does not show a highly specific or diagnostic picture. It typically shows a predominantly mononuclear inflammation that may range between mild portal infiltrate with or without interface hepatitis and diffuse panlobular inflammation with prominent perivenular infiltrate or confluent necrosis. Scattered plasma cells and occasional eosinophils may also occur [23,31,122,123]. However, the lack of plasma cell predominance in the lymphocytic infiltrate, which is a classic hallmark of AIH, may help differentiate between ILICI and idiopathic AIH [122]. In one study which compared ILICI to idiopathic AIH, ILICI was associated with less zone-selective necrosis and fewer $CD20^+$ B cells and $CD4^+$ T cells compared to AIH [31]. The less common cholestatic injury of ILICI may show a mononuclear infiltrate in portal tracts that is centered around bile ducts and bile ductular proliferation, consistent with primary injury to bile ducts or acute cholangitis [23,25]. A recent single center study reported distinct histopathological patterns for anti-CTLA4 and anti-PD-1/PD-L1 agents, with anti-CTLA4 drugs inducing a specific pattern of granulomatous hepatitis associated with severe lobular necrotic and inflammatory activity, fibrin deposits and central vein endothelialitis and a more heterogeneous histological pattern in the case of hepatotoxicity related to anti-PD-1/PD-L1 agents [34].

ILICI usually resolves within 4–6 weeks with interruption/discontinuation of the ICI and appropriate immunosuppressive treatment (see below) [7,21,33]. Most guidelines agree that if the serum ALT level fails to decrease substantially within 4–6 weeks of treatment for ILICI, alternative diagnoses must be reconsidered, and a diagnostic assessment should be repeated including, if possible, a liver biopsy [7,21].

### 6.1. Consensus and recommendations

31. In patients with or without hepatic metastases and normal or near normal baseline serum ALT (< 1.5x ULN), an increase of ALT to ≥3x ULN should prompt an evaluation for possible causes including possible ILICI versus tumor progression (Table 3).
32. In patients with or without hepatic metastases and elevated baseline serum ALT (≥1.5x ULN), an increase of ALT to ≥2x baseline should prompt an evaluation for possible causes including possible ILICI versus tumor progression (Table 3).
33. In patients with a normal baseline serum ALP, an increase of predominantly ALP to ≥2x ULN should trigger an evaluation for possible causes including cholestatic ILICI, tumor progression, biliary obstruction, systemic infection, bone disease, or DILI due to a concomitant medication.
34. In patients with an elevated baseline ALP, an increase of ALP to ≥2x baseline, should prompt an evaluation for possible causes including cholestatic ILICI, tumor progression, biliary obstruction, systemic infection, bone disease, or DILI due to a concomitant medication.
35. In patients with a treatment emergent serum ALP elevation without a significant elevation in serum ALT, other causes (e.g., worsening of hepatic or bone metastases, biliary obstruction) are more likely to be the cause than ILICI.
36. If serum AST increases with a less pronounced increase in serum ALT, alternative causes other than ILICI, should be sought, including muscle injury and alcohol related liver disease.
37. Failure to respond to discontinuation of ICIs and initiation of corticosteroid therapy within 4–6 weeks should warrant a repeat evaluation for other possible causes of liver injury and consideration of a liver biopsy.
38. ILICI patients typically do not have elevated titers of serum autoantibodies (e.g., ANA and ASMA) or increased serum IgG levels.

High titers of serum autoantibodies are more indicative of idiopathic AIH and should warrant further evaluation (including a possible liver biopsy) and appropriate follow-up for idiopathic AIH.

39. Liver biopsy typically is not required for the diagnosis of ILICI, but it can be helpful in patients who fail to respond to conventional therapy, or for those in whom the diagnosis is doubtful due to an atypical presentation or clinical course.
40. Liver biopsy may be helpful in distinguishing between ILICI and idiopathic AIH.
41. In a patient receiving combination treatment, a liver biopsy may be helpful in distinguishing between ILICI and DILI caused by a non-ICI drug.
42. It is recommended to save serum samples for testing for rare causes of liver injury. The collection of genomic DNA from patients with liver injury is encouraged in order to perform relevant testing for potential genetic susceptibility markers at a later date.

## 7. ILICI management: ICIs interruption and pharmacological treatment

### 7.1. General considerations

In contrast to most other DILI types, the recommended management of ILICI involves not only interruption/discontinuation of the suspected culprit drug, but often initiation of immunosuppressive therapy with corticosteroids such as methyl prednisolone or its equivalent (Tables 1 and 2) [7–9,21,33]. It is important to note that current management recommendations have been derived largely from practices employed in registration trials and are not derived from randomized controlled datasets. In most cases, management recommendations are based on changes in serum ALT, AST and TBL rather than ALP, since an isolated ALP elevation is often related to the underlying malignancy and less commonly due to ILICI [7,8,21]. Moreover, there are limited published data regarding management of ILICI in patients who develop isolated serum ALP elevation during ICI treatment. Generally, the use of serum ALT is preferred over AST due to its higher hepatic specificity. Typically, ILICI resolves within 4–6 weeks of interrupting ICI treatment and initiating corticosteroids, although occasionally, abnormal hepatic biochemical test persist or worsen despite these measures. In cases of ILICI worsening, second line therapy in clinical trial protocols and in clinical practice has consisted of a course of mycophenolate mofetil (MMF) in addition to corticosteroids [7,8,21,33]. In rare case reports, use of third line immunosuppressive therapy has been employed, including anti-thymocyte globulin (ATG), calcineurin inhibitors, rituximab, and others [125–127]. In general, there is insufficient prospective evidence to support one immunosuppressive therapeutic approach over another. Consequently, most drug developers and professional societies have based their practices on empiric considerations, and expert-consensus, often in alignment with prior ICI clinical trial protocols. In a few reports, patients with grade 3 ILICI experienced spontaneous resolution after withholding ICI treatment without initiation of corticosteroid therapy [34,128].

The following is a summary of the practices adopted in many ICI clinical trial protocols, which are endorsed by most of the clinical guidelines. Based on the IQ DILI IWG consensus, serum ALT is used as the predominant biomarker in management recommendations, since it is considered more specific for liver injury and more strongly associated with hepatocellular DILI than is serum AST.

### 7.2. Management of study participants with normal or near normal baseline serum ALT (< 1.5x ULN) (Table 1)

**Grade 1 ALT elevation (ALT > ULN-3x ULN):** Most clinical trial protocols and guidelines call for closer monitoring (e.g., weekly or bi-weekly) for signs and symptoms of liver injury and hepatic biochemical tests, including serum ALT, AST, ALP, TBL, and DBL [7,8,21,129]. A detailed medical history should be obtained, including concomitant medications, over the counter products, alcohol or other substance abuse, as well as herbal and dietary supplements. Most guidelines do not call for treatment interruption with grade 1 changes [7,8,21,129]. Frequency of monitoring can be adjusted based on extent and trajectory of ALT elevation.

**Grade 2 serum ALT elevation (ALT > 3-5x ULN):** Most clinical trials and guidelines recommend withholding ICI treatment and initiating close monitoring for signs and symptoms of liver injury and hepatic biochemical tests, including serum ALT, AST, ALP, TBL, and DBL twice weekly. Suppl Table S3 outlines examples of treatment interruption and discontinuation criteria used in ICIs clinical trials. If ALT returns to baseline values within 1–2 weeks, ICI treatment can be resumed with close monitoring of hepatic biochemical tests. Persistent grade 2 elevation lasting longer than 1–2 weeks, calls for evaluation for alternative causes of liver injury (Table 3), and initiation of oral corticosteroid therapy (prednisolone, methylprednisolone or equivalent) at a dose of 0.5–1 mg/kg/day. If the abnormality improves to grade 1, the dose of corticosteroids can be tapered over 4–6 weeks. Upon improvement, ICI therapy may be resumed once the dose of corticosteroid reaches 10 mg/day. If no improvement occurs after initiation of corticosteroids, the corticosteroid dose should be increased to 2 mg/kg/day (prednisolone, methylprednisolone, or equivalent) and the route of administration may be switched to intravenous (IV) methylprednisolone. In addition, permanent discontinuation of ICI therapy should be considered [7–9,21,62].

**Grade 3 or 4 serum ALT elevation (> 5x ULN):** Most clinical trials and guidelines recommend withholding of ICI therapy and initiating corticosteroid therapy (prednisolone, methylprednisolone or equivalent) at 1–2 mg/kg/day [7–9,21,62,129]. Oral prednisolone/methylprednisolone at a dose of 1 mg/kg/day is recommended for grade 3 elevation, while 2 mg/kg/day of IV methylprednisolone is recommended for grade 4 elevations. If there is no response to corticosteroids within 2–3 days, most guidelines recommend the addition of mycophenolate mofetil 500–1000 mg twice daily, consultation with a hepatologist, and consideration of a liver biopsy [7–9,14,21,129]. There are insufficient data to support a specific third-line immunosuppressive therapy. Successful use of anti-thymocyte globulin (ATG) has been reported in a few cases [130–132]. Other agents that have been used empirically, include calcineurin inhibitors (tacrolimus or cyclosporine), rituximab (anti-CD20 monoclonal antibody), and tocilizumab (anti-interleukin-6 receptor monoclonal antibody) [125,133]. Despite limited evidence, most experts do not recommend the use of infliximab (anti-tumor necrosis factor alpha monoclonal antibody) given the concern of hepatotoxicity [7,9,21]. A few groups have suggested a more selective use of corticosteroids in some patients with grade 3 ILICI, especially when liver histology shows less severe injury; however, more data are needed before this approach can be widely adopted [18,34].

While a thorough evaluation for alternative causes of liver injury should be initiated as soon as possible, there is strong agreement among drug developers and published guidelines that immunosuppressive therapy, if needed, should be initiated without delay in the absence of any other apparent cause [7,8,21].

In general, most guidelines strongly agree that ICI therapy be permanently discontinued whenever the serum ALT elevation is > 10x ULN, or if the ALT elevation is accompanied by increase in TBL > 2x ULN (see rechallenge below) [7–9,21].

**Elevated TBL:** Generally, most guidelines agree that patients with grade 2 serum ALT elevation, who have a concomitant TBL elevation ≥2x ULN should be managed as grade 3–4 ALT elevation, unless the bilirubin elevation is caused by Gilbert's syndrome [7–9,21].

### 7.3. Management of study participants with elevated baseline serum ALT (≥1.5x ULN) (Table 2)

Patients with metastatic cancer or primary hepatic tumors frequently have abnormal hepatic biochemical tests at the time of enrollment. In such cases the thresholds for hepatic monitoring, treatment discontinuation and initiation of immunosuppression therapy may be difficult to implement. Under these circumstances, it has been suggested to use multiples of baseline serum ALT rather than multiples of ULN as a threshold for suspecting DILI [35,36,116,117].

In the absence of large prospective comparative data, there is little evidence to support specific thresholds for initiation of close monitoring, withholding of ICI treatment and initiation of immunosuppressive therapy, although several approaches have been proposed for patients with pre-existing liver diseases [35,36,116,117]. Table 2 outlines an approach suggested by the IQ DILI IWG for patients with elevated baseline serum ALT≥ 1.5x ULN.

### 7.4. Drug rechallenge

While a general discussion of drug rechallenge in patients with DILI or ILICI is beyond the scope of this publication, it is important to note that close monitoring is critically important in these circumstances, as liver injury may recur rapidly and may be difficult to control.

Most ICI clinical trials and guidelines have allowed restarting treatment (also known as rechallenge) in patients with grade 2 serum ALT elevation which returned to baseline after treatment-interruption, with or without corticosteroid treatment. While most clinical trials have avoided resuming treatment in patients with grade 3 or 4 ALT elevation who returned to baseline, more recent clinical trials and guidelines have allowed restarting treatment if a grade 3 ALT elevation did not exceed 10x ULN and was not accompanied by elevated TBL of > 2x ULN [7,8,21,62]. In a retrospective study from MD Anderson Cancer Center, 31 patients restarted ICI therapy after ILICI had improved to ≤ grade 1 ALT (< 3x ULN). Twenty-nine of these patients had grade 3, and 2 had grade 4 ILICI. Restarting of ICI therapy led to recurrent ILICI in 8 (26%) of the cases [33]. All the 8 cases initially had grade 3 ILICI, and in all 8, ICIs were stopped permanently after recurrent ILICI [33]. In another retrospective study, resumption of ICIs (specifically of anti–PD-1 therapy) led to recurrent ILICI in 17% of the cases [134]. These reports highlight the need to refine the management of specific ILICI cases, however additional prospective data are necessary.

In special circumstances, when ICI treatment is critical to the patient's anti-cancer regimen, it has been recommended that the pros/benefits and cons/risk of restarting the treatment be discussed with the patient and/or his or her health-care proxy and that written informed consent be obtained prior to restarting of ICI therapy [33,135].

### 7.5. Consensus and recommendations

43. Restarting ICI therapy may be considered in patients with ILICI who had grade 2 serum ALT elevation and normal TBL that returned to baseline values.
44. Restarting of ICI therapy may be considered in patients with ILICI who had grade 3 serum ALT elevation without a significant elevation in TBL (unless diagnosed with Gilbert's syndrome), provided ALT did not exceed 10x ULN and returned to baseline value.
45. A liver biopsy may be helpful in deciding on whether ICI therapy can be resumed after resolution of ILICI. Less severe histologic disease has been cited as a reason to restart therapy after resolution of ILICI.
46. There are limited data on the efficacy of prophylactic corticosteroid therapy administered prior to resumption of ICI therapy for prevention of recurrent ILICI.
47. In patients who resume ICI treatment after resolution of ILICI it is recommended to monitor liver tests at least weekly for the first 2 months and every 2 weeks for the 3rd month. Monitoring frequency may change based on the severity of preceding ILICI.
48. In special circumstances, it is recommended that written informed consent detailing the benefit and risk of restarting the treatment, be obtained prior to resuming ICI therapy.

## 8. Summary

The number of clinical trials using ICIs as single agents or in combination with other anti-tumor treatments is increasing rapidly and there is a growing need for clear and consistent practices pertaining to detection, assessment, and management of ILICI during drug development. Early detection and management of ILICI are paramount and may have a critical impact on the success of immunotherapy. This publication provides a framework for recommendations based on the collaborative work of the IQ DILI initiative with experts from academia and other experts in the DILI field. Future analysis of cross industry clinical trial data may provide crucial information to further understand ILICI and improve our approach to its assessment and management.

## Financial Support

No financial support was received for this manuscript.

## Declaration of competing interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2020.102514.

## References

[1] P. Sharma, J.P. Allison, Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential, Cell (2015) 205–214, https://doi.org/10.1016/j.cell.2015.03.030.
[2] D.L. Suzman, L. Pelosof, A. Rosenberg, M.I. Avigan, Hepatotoxicity of immune checkpoint inhibitors: an evolving picture of risk associated with a vital class of immunotherapy agents, Liver Int. 38 (2018) 976–987, https://doi.org/10.1111/liv.13746.
[3] P. Serrano, M. Hartmann, E. Schmitt, P. Franco, G. Amexis, J. Gross, et al., Clinical development and initial approval of novel immune checkpoint inhibitors in oncology: insights from a global regulatory perspective, Clin. Pharmacol. Ther. 15 (2019) 582–597, https://doi.org/10.1002/cpt.1123.
[4] A. Markham, S. Duggan, Cemiplimab: first global approval, Drugs 78 (2018) 1841–1846, https://doi.org/10.1007/s40265-018-1012-5.
[5] E. Vick, D. Mahadevan, Programming the immune checkpoint to treat hematologic malignancies, Expet Opin. Invest. Drugs 25 (2016) 755–770, https://doi.org/10.1080/13543784.2016.1175433.
[6] J. Villadolid, A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities, Transl. Lung Cancer Res. 4 (2015) 560–575, https://doi.org/10.3978/j.issn.2218-6751.2015.06.06.
[7] J.B.A.G. Haanen, F. Carbonnel, C. Robert, K.M. Kerr, S. Peters, J. Larkin, et al., Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 28 (2017) 119–142, https://doi.org/10.1093/annonc/mdx225.
[8] I. Puzanov, A. Diab, K. Abdallah, C.O. Bingham, C. Brogdon, R. Dadu, et al., Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) toxicity management working group, J. Immunother. Cancer. 5 (2017) 95, https://doi.org/10.1186/s40425-017-0300-z.
[9] J.A. Thompson, B.J. Schneider, J. Brahmer, S. Andrew, P. Armand, S. Bhatia, et al., Management of immunotherapy-related toxicities, version 1.2019, J. Natl. Compr. Canc. Netw. 17 (2019) 255–289, https://doi.org/10.6004/jnccn.2019.0013.
[10] J.H. Hoofnagle, E.S. Björnsson, Drug-induced liver injury- types and phenotypes, N. Engl. J. Med. 381 (2019) 264–273, https://doi.org/10.1056/NEJMra1816149.
[11] J.S. Weber, R. Dummer, V. de Pril, C. Lebbé, F.S. Hodi, Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab, Cancer, 2013, pp. 1675–1682.
[12] S. Sarmen, S. Tara, Acute liver failure from anti-PD-1 antibody nivolumab in a patient with metastatic lung squamous cell carcinoma, Austin Oncol 1 (2016) 1–3.
[13] F. Alessandrino, S.H. Tirumani, K.M. Krajewski, A.B. Shinagare, J.P. Jagannathan, N.H. Ramaiya, et al., Imaging of hepatic toxicity of systemic therapy in a tertiary

cancer centre: chemotherapy, haematopoietic stem cell transplantation, molecular targeted therapies, and immune checkpoint inhibitors, Clin. Radiol. 72 (2017) 521-533, https://doi.org/10.1016/j.crad.2017.04.003.
[14] R. Tanaka, Y. Fujisawa, I. Sae, H. Maruyama, S. Ito, N. Hasegawa, et al., Severe hepatitis arising from ipilimumab administration, following melanoma treatment with nivolumab, Jpn. J. Clin. Oncol. 47 (2017) 175–178, https://doi.org/10.1093/jjco/hyw167.
[15] B.M. Huffman, L.A. Kottschade, P.S. Kamath, S.N. Markovic, Hepatotoxicity after immune checkpoint inhibitor therapy in melanoma: natural progression and management, Am. J. Clin. Oncol. 41 (2018) 760–765, https://doi.org/10.1097/COC.0000000000000374.
[16] Y. Wang, S. Zhou, F. Yang, X. Qi, X. Wang, x Guan, et al., Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials. A systematic review and meta-analysis, JAMA Oncol 5 (2019) 1008–1019, https://doi.org/10.1001/jamaoncol.2019.0393.
[17] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, et al., Combined nivolumab and ipilimumab or monotherapy in untreated melanoma, N. Engl. J. Med. 373 (2015) 23–34, https://doi.org/10.1056/NEJMoa1504030.
[18] J.J. Jennings, R. Mandaliyaa, A. Nakshabandib, J.H. Lewis, Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies, Expet Opin. Drug Metabol. Toxicol. 15 (2019) 231–244, https://doi.org/10.1080/17425255.2019.1574744.
[19] L. Spain, S. Diem, J. Larkin, Management of toxicities of immune checkpoint inhibitors, Canc. Treat Rev. 44 (2016) 51–60, https://doi.org/10.1016/j.ctrv.2016.02.001.
[20] S. Champiat, O. Lambotte, E. Barreau, E. Belkhir, A. Berdelou, F. Carbonnel, et al., Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper, Ann. Oncol. 27 (2016) 559–574, https://doi.org/10.1093/annonc/mdv623.
[21] J.R. Brahmer, C. Lacchetti, B.J. Schneider, M.B. Atkins, K.J. Brassil, J.M. Caterino, et al., Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline, J. Clin. Oncol. 36 (2018) 1714–1768, https://doi.org/10.1200/JOP.18.00005.
[22] IQ DII Initiative, https://www.iqdili.org, (2020) , Accessed date: 2 February 2020.
[23] K.W. Kim, N.H. Ramaiya, K.M. Krajewski, J.P. Jagannathan, S.H. Tirumani, A. Srivastava, et al., Ipilimumab associated hepatitis: imaging and clinicopathologic findings, Invest. N. Drugs 31 (2013) 1071–1077, https://doi.org/10.1007/s10637-013-9939-6.
[24] F. Gelsomino, G. Vitale, A. D'Errico, C. Bertuzzi, P. Andreone, A. Ardizzoni, et al., Nivolumab-induced cholangitic liver disease: a novel form of serious liver injury, Ann. Oncol. 28 (2017) 671–672, https://doi.org/10.1093/annonc/mdw649.
[25] H. Kawakami, J. Tanizaki, K. Tanaka, K. Haratani, H. Hayashi, M. Takeda, et al., Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer, Invest. N. Drugs 35 (2017) 529–536, https://doi.org/10.1007/s10637-017-0453-0.
[26] I. Tsung, R. Dolan, C.D. Lao, L. Fecher, K. Riggenbach, A. Yeboah-Korang, et al., Liver injury is most commonly due to hepatic metastases rather than drug hepatotoxicity during pembrolizumab immunotherapy, Aliment. Pharmacol. Ther. 50 (2019) 800–808, https://doi.org/10.1111/apt.15413.
[27] K.C. Kähler, A. Hauschild, Treatment and side effect management of CTLA-4 antibody therapy in metastatic melanoma, JDDG 9 (2011) 277–286, https://doi.org/10.1111/j.1610-0387.2010.07568.x.
[28] Y.M. Kong, J.C. Flynn, Opportunistic autoimmune disorders potentiated by immune-checkpoint inhibitors anti-CTLA-4 and anti-PD-1, Front. Immunol. 5 (2014) 1–8, https://doi.org/10.3389/fimmu.2014.00206.
[29] G.K. Philips, M. Atkins, Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies, Int. Immunol. 27 (2014) 39–46, https://doi.org/10.1093/intimm/dxu095.
[30] E.D. Deeks, Pembrolizumab: a review in advanced melanoma, Drugs 76 (2016) 375–386, https://doi.org/10.1007/s40265-016-0543-x.
[31] Y. Zen, M.M. Yeh, Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury, Mod. Pathol. 31 (2018) 965–973, https://doi.org/10.1038/s41379-018-0013-y.
[32] D.M. Chascsa, J. Rakela, Knowns and unknowns: the safety and efficacy of cancer immunotherapy in chronic liver disease, Current Hepatology Reports 17 (2018) 153–155, https://doi.org/10.1007/s11901-018-0408-8.
[33] E.D. Miller, H. Abu-Sbeih, B. Styskel, G.M. Nogueras Gonzalez, B. Blechacz, A. Naing, et al., Clinical characteristics and adverse impact of hepatotoxicity due to immune checkpoint inhibitors, Am. J. Gastroenterol. (2019) online. hpps://doi.org/10.14309/ajg.0000000000000398.
[34] E. De Martin, J.M. Michot, B. Papouin, A. Marabelle, C. Guettier, D. Samuel, et al., Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors, J. Hepatol. 68 (2018) 1181–1190, https://doi.org/10.1016/j.jhep.2018.01.033.
[35] FDA, Guidance for industry, Drug-induced Livery Injury: Premarketing Clinical Evaluation, (2009) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf , Accessed date: 20 July 2019.
[36] G.P. Aithal, P.B. Watkins, R.J. Andrade, D. Larrey, M. Molokhia, H. Takikawa, et al., Case definition and phenotype standardization in drug-induced liver injury, Clin. Pharmacol. Ther. 89 (2011) 806–815, https://doi.org/10.1038/clpt.2011.58.
[37] M.I. Avigan, E.S. Bjornsson, M. Pasanen, C. Cooper, R.J. Andrade, P.B. Watkins, et al., Liver safety assessment: required data elements and best practices for data collection and standardization in clinical trials, Drug Saf. 37 (2014), https://doi.org/10.1007/s40264-014-0183-6 S19–S31.
[38] A.D. Ricart, Drug-induced liver injury in oncology, Ann. Oncol. 28 (2017) 2013–2020, https://doi.org/10.1093/annonc/mdx158.
[39] L. Dara, Z.X. Liu, N. Kaplowitz, Mechanisms of adaptation and progression in idiosyncratic drug induced liver injury, clinical implications, Liver Int. 36 (2016) 158–165, https://doi.org/10.1111/liv.12988.
[40] Z. Bankowski, R. Bruppacher, Gallagher J. CrusiusI, G. Kremer, J. Venulet, Council for international organizations of medical sciences (CIOMS). Liver and biliary system disorders (SOC 0700), Reporting Adverse Drug Reaction. Definitions of Terms and Criteria for Their Use, (1999) Switzerland.
[41] National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, (2017) Accessed https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf , Accessed date: 5 February 2020.
[42] J.R. Senior, Evolution of the Food and Drug Administration approach to liver safety assessment for new drugs: current status and challenges, Drug Saf. 37 (2014), https://doi.org/10.1007/s40264-014-0182-7 S9–S17.
[43] C.D. Tweed, G.H. Wills, A.M. Crook, R. Dawson, A.H. Diacon, C.E. Louw, et al., Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study, BMC Med. 16 (2018) 1–10, https://doi.org/10.1186/s12916-018-1033-7.
[44] P.B. Watkins, H.J. Zimmerman, M.J. Knapp, et al., Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease, J. Am. Med. Assoc. 271 (1994) 992–998, https://doi.org/10.1001/jama.1994.03510370044030.
[45] J.R. Brahmer, S.S. Tykodi, L.Q.M. Chow, W.J. Hwu, TopalianSL, P. Hwu, et al., Safety and activity of anti-PD-L1 antibody in patients with advanced cancer, N. Engl. J. Med. 366 (2012) 2455–2465, https://doi.org/10.1056/NEJMoa1200694.
[46] O. Hamid, C. Robert, A. Daud, F.S. Hodi, W.J. Hwu, R. Kefford, et al., Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma, N. Engl. J. Med. 369 (2013) 134–144, https://doi.org/10.1056/NEJMoa1305133.
[47] S.L. Topalian, M. Sznol, D.F. McDermott, H.M. Kluger, R.D. Carvajal, W.H. Sharfman, et al., Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab, J. Clin. Oncol. 32 (2014) 1020–1030, https://doi.org/10.1200/JCO.2013.53.0105.
[48] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, et al., Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer, N. Engl. J. Med. 373 (2015) 1627–1639, https://doi.org/10.1056/NEJMoa1507643.
[49] J. Larkin, C.D. Lao, W.J. Urba, D.F. McDermott, C. Horak, J. Jiang, et al., Efficacy and safety of nivolumab in patients with BRAF V600 mutant and BRAF wild-type advanced melanoma: a pooled analysis of 4 clinical trials, JAMA Oncol 1 (2015) 433–440, https://doi.org/10.1001/jamaoncol.2015.1184.
[50] E.B. Garon, N.A. Rizvi, R. Hui, N. Leighl, A.S. Balmanoukian, J.P. Eder, et al., Pembrolizumab for the treatment of non–small-cell lung cancer, N. Engl. J. Med. 372 (2015) 2018–2028, https://doi.org/10.1056/NEJMoa1501824.
[51] R.J. Motzer, B.I. Rini, D.F. McDermott, B.G. Redman, T.M. Kuzel, M.R. Harrison, et al., Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial, J. Clin. Oncol. 33 (2015) 1430–1437, https://doi.org/10.1200/JCO.2014.59.0703.
[52] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, et al., Pembrolizumab versus ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (2015) 2521–2532, https://doi.org/10.1056/NEJMoa1503093.
[53] C. Robert, G.V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, et al., Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (2015) 320–330, https://doi.org/10.1056/NEJMoa1412082.
[54] Y.Y. Janjigian, J. Bendell, E. Calvo, J.W. Kim, P.A. Ascierto, P. Sharma, et al., CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer, J. Clin. Oncol. 36 (2018) 2836–2844, https://doi.org/10.1200/JCO. 2017.76.6212.
[55] W. Wang, P. Lie, M. Guo, J. He, Risk of hepatotoxicity in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis of published data, Int. J. Canc. 141 (2017) 1018–1028, https://doi.org/10.1002/ijc.30678.
[56] D.P. Carbone, M. Reck, L. Paz-Ares, B. Creelan, L. Horn, M. Steins, et al., First-line nivolumab in stage IV or recurrent non-small-cell lung cancer, N. Engl. J. Med. 376 (2017) 2415–2426, https://doi.org/10.1056/NEJMoa1613493.
[57] C. Robert, A. Ribas, J.D. Wolchok, F.S. Hodi, O. Hamid, R. Kefford, et al., Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trail, Lancet 384 (2014) 1109–1117, https://doi.org/10.1016/S0140-6736(14)60958-2.
[58] J.S. Weber, S.P. D'Angelo, D. Minor, F.S. Hodi, R. Gutzmer, B. Neyns, et al., Nivolumab versus chemotherapy in patients with advanced melanoma who progress after anti-CTLA-4 treatment (checkmate 037): a randomised, controlled, open-label, phase 3 trial, Lancet Oncol. 16 (2015) 375–384, https://doi.org/10.1016/S1470-2045(15)70076-8.
[59] F.S. Hodi, S.J. O'Day, D.F. McDermott, R.W. Weber, J.H. Sosman, J.B. Haanen, et al., Improved survival with ipilimumab in patients with metastatic melanoma, N. Engl. J. Med. 363 (2010) 711–723, https://doi.org/10.1056/NEJMoa1003466.
[60] L. Calabrò, A. Morra, E. Fonsatti, O. Cutaia, G. Amato, D. Giannarelli, et al., Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial, Lancet Oncol. 14 (2013) 1104–1111, https://doi.org/10.1016/S1470-2045(13)70381-4.
[61] J. Brahmer, K.L. Reckamp, P. Baas, L. Crinò, W.E.E. Eberhardt, E. Poddubskaya, et al., Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer, Engl J Med 373 (2015) 123–135, https://doi.org/10.1056/NEJMoa1504627.

[62] Keytruda (Pembrolizumab) Label, Accessed https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514s040lbl.pdf, (2019) , Accessed date: 1 February 2020.

[63] J.S. Weber, K.C. Kähler, A. Hauschild, Management of immune-related adverse events and kinetics of response with ipilimumab, J. Clin. Oncol. 30 (2012) 2691–2697, https://doi.org/10.1200/JCO.2012.41.6750.

[64] A.M. Di Giacomo, M. Biagioli, M. Maioa, The emerging toxicity profiles of anti–CTLA-4 antibodies across clinical indications, Semin. Oncol. 37 (2010) 499–507, https://doi.org/10.1053/j.seminoncol.2010.09.007.

[65] R. Cheng, A. Cooper, J. Kench, G. Watson, W. Bye, C. McNeil, et al., Ipilimumab-induced toxicities and the gastroenterologist, J. Gastroenterol. Hepatol. 30 (2015) 657–666, https://doi.org/10.1111/jgh.12888.

[66] D.Y. Wang, J.E. Salem, J.V. Cohen, S. Chandra, C. Menzer, F. Ye, et al., Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis, JAMA Oncol 4 (2018) 1721–1728, https://doi.org/10.1001/jamaoncol.2018.3923.

[67] J.D. Wolchok, B. Neyns, G. Linette, S. Negrier, J. Lutzky, L. Thomas, et al., Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study, Lancet Oncol. 11 (2010) 155–164, https://doi.org/10.1016/S1470-2045(09)70334-1.

[68] A. Ribas, F.S. Hodi, M. Callahan, C. Konto, J. Wolchok, Hepatotoxicity with combination of vemurafenib and ipilimumab, N. Engl. J. Med. 368 (2013) 1365–1366, https://doi.org/10.1056/NEJMc1302338.

[69] P.A. Ascierto, M. Del Vecchio, C. Robert, A. Mackiewicz, V. Charion-Sileni, A. Arance, et al., Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial, Lancet Oncol. 18 (2017) 611–622, https://doi.org/10.1016/S1470-2045(17)30231-0.

[70] C. Robert, L. Thomas, I. Bondarenko, S. O'Day, J. Weber, C. Garbe, et al., Ipilimumab plus dacarbazine for previously untreated metastatic melanoma, N. Engl. J. Med. 364 (2011) 2517–2526, https://doi.org/10.1056/NEJMoa1104621.

[71] M. Sznol, P.F. Ferrucci, D. Hogg, M.B. Atkins, P. Wolter, M. Guidoboni, et al., Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma, J. Clin. Oncol. 35 (2017) 3815–3822, https://doi.org/10.1200/JCO. 2016.72.1167.

[72] A. Mak, J. Uetrecht, The combination of anti-CTLA-4 and PD1-/- mice unmasks the potential of isoniazid and nevirapine to cause liver injury, Chem. Res. Toxicol. 28 (2015) 2287–2291, https://doi.org/10.1021/acs.chemrestox.5b00305.

[73] M.A. Postow, J. Chesney, A.C. Pavlick, C. Robert, K. Grossmann, D. McDermott, et al., Nivolumab and ipilimumab versus ipilimumab in untreated melanoma, N. Engl. J. Med. 372 (2015) 2006–2017, https://doi.org/10.1056/NEJMoa1414428.

[74] J.S. Weber, J.A. Thompson, O. Hamid, D. Minor, A. Amin, I. Ron, et al., A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma, Clin. Canc. Res. 15 (2009) 5591–5598, https://doi.org/10.1158/1078-0432.CCR-09-1024.

[75] S.J. O'Day, M. Maio, V. Chiarion-Sileni, T.F. Gajewski, H. Pehamberger, I.N. Bondarenko, et al., Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study, Ann. Oncol. 21 (2010) 1712–1717, https://doi.org/10.1093/annonc/mdq013.

[76] K. Sawada, H. Hayashi, S. Nakajima, T. Hasebe, M. Fujiya, T. Okumura, Non-alcoholic fatty liver disease is a potential risk factor forliver injury caused by immune checkpoint inhibitor, J. Gastroenterol. Hepatol. 35 (2020) 1042–1048, https://doi.org/10.1111/jgh.14889.

[77] S. Ravi, K. Spencer, M. Ruisi, N. Ibrahim, J.J. Luke, J.A. Thompson, et al., Ipilimumab administration for advanced melanoma in patients with pre-existing hepatitis B or C infection: a multicenter, retrospective case series, J Immunother Cancer 22 (2014) 33–40, https://doi.org/10.1186/s40425-014-0033-1.

[78] R. Rai, O.M. Ezeoke, J.L. McQuade, L. Zimmer, C. Koo, J.J. Park, et al., Immunotherapy in patients with concurrent solid organ transplant, HIV, and hepatitis B and C, Ann. Oncol. 28 (2017) 403–427, https://doi.org/10.1093/annonc/mdx376.

[79] A.B. El-Khoueiry, B. Sangro, T. Yau, T.S. Crocenz, M. Kudo, C. Hsu, et al., Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial, Lancet 389 (2017) 2492–2502, https://doi.org/10.1016/S0140-6736(17)31046-2.

[80] A.X. Zhu, R.S. Finn, J. Edeline, S. Cattan, S. Ogasawara, D. Palmer, et al., Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial, Lancet Oncol. 19 (2018) 940–952, https://doi.org/10.1016/S1470-2045(18)30351-6.

[81] Opdivo (Nivolumab) Label, Accessed https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125554s070lbl.pdf, (2019) , Accessed date: 10 February 2020.

[82] Fda Center for Drug Evaluation and Research, Division Director Summary Review, (2014) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000SumR.pdf , Accessed date: 20 January 2020.

[83] J. Liu, E. Zhang, Z. Ma, W. Wu, A. Kosinska, X. Zhang, et al., Enhancing virus-specific immunity in vivo by combining therapeutic vaccination and PD-L1 blockade in chronic hepadnaviral infection, PLoS Pathog. 10 (2014) e1003856, , https://doi.org/10.1371/journal.ppat.1003856.

[84] M.J. Fuller, B. Callendret, B. Zhu, G.J. Freeman, D.L. Hasselschwert, W. Satterfield, et al., Immunotherapy of chronic hepatitis C virus infection with antibodies against programmed cell death-1 (PD-1), Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 15001–15006, https://doi.org/10.1073/pnas.1312772110.

[85] B. Sangro, C. Gomez-Martin, M. de la Mata, M. Iñarrairaegui, E. Garralda, P. Barrera, et al., A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C, J. Hepatol. 59 (2013) 81–88, https://doi.org/10.1016/j.jhep.2013.04.002.

[86] D. Davar, M. Wilson, C. Pruckner, J.M. Kirkwood, PD-1 blockade in advanced melanoma in patients with Hepatitis C and/or HIV, Case Rep Oncol Med (2015) 1–5, https://doi.org/10.1155/2015/737389.

[87] J.A. Beaver, G. Ison, R. Pazdur, Reevaluating eligibility criteria- balancing patient protection and participation in oncology trials, N. Engl. J. Med. 376 (2017) 1504-1505, https://doi.org/10.1056/NEJMp1615879.

[88] E.S. Kim, S.S. Bruinooge, S. Roberts, G. Ison, N.U. Lin, L. Gore, et al., Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and friends of cancer research joint research statement, J. Clin. Oncol. 35 (2017) 3737-3744, https://doi.org/10.1200/JCO.2017.73.7916.

[89] P. Biondani, E. De Martin, D. Samuel, Safety of an anti-PD-1 immune checkpoint inhibitor in a liver transplant recipient, Ann. Oncol. 29 (2018) 286–287, https://doi.org/10.1093/annonc/mdx548.

[90] A. Varkaris, D.W. Lewis, F.W. Nugent, Preserved liver transplant after PD-1 pathway inhibitor for hepatocellular carcinoma, Am. J. Gastroenterol. 112 (2017) 1895, https://doi.org/10.1038/ajg.2017.387 –6.

[91] N. Abdel-Wahab, H. Safa, A. Abudayyeh, D.H. Johnson, V.A. Trinh, C.M. Zobniw, et al., Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature, J. Immun. Canc. 7 (2019) 1–10, https://doi.org/10.1186/s40425-019-0585-1.

[92] Herbst RHerbsS, P. Baas, D.W. Kim, E. Felip, J.L. Pérez-Gracia, J.Y. Han, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (2016) 1540–1550, https://doi.org/10.1016/S0140-6736(15)01281-7.

[93] R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, et al., Nivolumab versus everolimus in advanced renal-cell carcinoma, N. Engl. J. Med. 373 (2015) 1803–1813, https://doi.org/10.1056/NEJMoa1510665.

[94] R.J. Motzer, N.M. Tannir, D.F. McDermott, O.A. Frontera, B. Melichar, T.K. Choueiri, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, N. Engl. J. Med. 378 (2018) 1277–1290, https://doi.org/10.1056/NEJMoa1712126.

[95] S.L. Topalian, F.S. Hodi, J.R. Brahmer, S.N. Gettinger, D.C. Smith, D.F. McDermott, et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer, N. Engl. J. Med. 366 (2012) 2443–2454, https://doi.org/10.1056/NEJMoa1200690.

[96] L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, et al., Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer, N. Engl. J. Med. 378 (2018) 2078–2092, https://doi.org/10.1056/NEJMoa1801005.

[97] M. Reck, D. Rodríguez-Abreu, A.G. Robinson, R. Hui, T. Csöszi, A. Fülöp, et al., Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, N. Engl. J. Med. 375 (2016) 1823–1833, https://doi.org/10.1056/NEJMoa1606774.

[98] J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.L. Lee, L. Fong, et al., Pembrolizumab as second-line therapy for advanced urothelial carcinoma (Keynote 045), N. Engl. J. Med. 376 (2017) 1015–1026, https://doi.org/10.1056/NEJMoa1613683.

[99] A. Ribas, I. Puzanov, R. Dummer, D. Schadendorf, O. Hamid, C. Robert, et al., Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (keynote-002): a randomised, controlled, phase 2 trial, Lancet Oncol. 16 (2015) 908–918, https://doi.org/10.1016/S1470-2045(15)00083-2.

[100] F.S. Hodi, J. Chesney, A.C. Pavlick, C. Robert, K.F. Grossmann, D.F. McDermott, et al., Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial, Lancet Oncol. 17 (2016) 1558–1568, https://doi.org/10.1016/S1470-2045(16)30366-7.

[101] A. Fretzayas, M. Moustaki, O. Liapi, T. Karpathios, Gilbert syndrome, Eur. J. Pediatr. 171 (2012) 11–15, https://doi.org/10.1007/s00431-011-1641-0.

[102] S. Kathemann, E. Lainka, H.A. Baba, P.F. Hoyer, P. Gemer, Gilbert's syndrome-a frequent cause of unconjugated hyperbilirubinemia in children after orthotopic liver transplantation, Pediatr. Transplant. 16 (2012) 201–204, https://doi.org/10.1111/j.1399-3046.2012.01662.x.

[103] M. Tio, R. Rai, M. Ogochukwu, O.M. Ezeoke, J.L. McQuade, L. Zimmer, C. Khoo, et al., Anti-PD-1/PD-L1 immunotherapy in patients with solid organ transplant, HIV or hepatitis B/C infection, Eur. J. Canc. 104 (2018) 137–144, https://doi.org/10.1016/j.ejca.2018.09.017.

[104] A. Rammohan, M.S. Reddy, M. Farouk, J. Vargese, M. Rela, Pembrolizumab for metastatic hepatocellular carcinoma following live donor liver transplantation: the silver bullet? Hepatology 67 (2018) 1166–1168, https://doi.org/10.1002/hep.29575.

[105] B. Raziorrouh, M. Heeg, P. Kurktschiev, W. Schraut, R. Zachoval, C. Wediner, et al., Inhibitory phenotype of HBV-specific CD4+ T-cells is characterized by high PD-1 expression but absent coregulation of multiple inhibitory molecules, PloS One 9 (2014) e105703, , https://doi.org/10.1371/journal.pone.0105703.

[106] E. Billerbeck, R. Wolfisberg, U. Fahnøe, J.W. Xiao, C. Quirk, J.M. Luna, et al., Mouse models of acute and chronic hepacivirus infection, Science 357 (2017) 204–208, https://doi.org/10.1126/science.aal1962.

[107] D.B. Johnson, R.J. Sullivan, P.A. Ott, M.S. Carlino, N.I. Khushalani, F. Ye, et al., Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders, JAMA Oncol 2 (2016) 234–240, https://doi.org/10.1001/jamaoncol.2015.4368.

[108] A.M. Menzies, D.B. Johnson, S. Ramanujam, V.G. Atkinson, A.N.M. Wong,

J.J. Park, et al., Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab, Ann. Oncol. 28 (2017) 368–376, https://doi.org/10.1093/annonc/mdw443.
[109] N. Abdel-Wahab, M. Shah, M.A. Lopez-Olivo, M.E. Suarez-Almazor, Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review, Ann InterReck n Med 168 (2018) 121–130, https://doi.org/10.7326/M17-2073.
[110] A. Gurung, D.N. Assis, T.R. McCarty, K.A. Mitchell, J.L. Boyer, D. Jain, Histologic features of autoimmune hepatitis: a critical appraisal, Hum. Pathol. 82 (2018) 51–60, https://doi.org/10.1016/j.humpath.2018.07.014.
[111] Imfinzi (Durvalumab) Label., https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761069s002lbl.pdf, (2018) , Accessed date: 21 January 2020.
[112] Yervoy (Ipilimumab) Label, Accessed https://packageinserts.bms.com/pi/pi_yervoy.pdf, (2018) , Accessed date: 21 January 2020.
[113] Bavencio (Avelumab) Label, Accessed https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf, (2017) , Accessed date: 21 January 2020.
[114] Tecentriq (Atezolizumab) Label, Accessed https://www.gene.com/download/pdf/tecentriq_prescribing.pdf, (2018) , Accessed date: 21 January 2020.
[115] M. Maio, A. Scherpereel, L. Calabrò, J. Aerts, S.C. Perez, A. Bearz, et al., Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial, Lancet Oncol. 18 (2017) 1261–1273, https://doi.org/10.1016/S1470-2045(17)30446-1.
[116] N. Chalasani, A. Regev, Drug-induced liver injury in patients with preexisting chronic liver disease in drug development: how to identify and manage? Gastroenterology 151 (2016) 1046–1051, https://doi.org/10.1053/j.gastro.2016.10.010.
[117] A. Regev, M. Palmer, M.I. Avigan, L. Dimick-Santos, W.R. Treem, J.F. Marcinak, et al., Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis, Aliment. Pharmacol. Ther. 49 (2019) 702–713, https://doi.org/10.1111/apt.15153.
[118] A. Regev, L.B. Seeff, M. Merz, S. Ormarsdottir, G.P. Aithal, J. Gallivan, et al., Causality assessment for suspected DILI during clinical phases of drug development, Drug Saf. 37 (2014) S47–S56, https://doi.org/10.1007/s40264-014-0185-4.
[119] S. Shantakumar, S. Landis, A. Lawton, C.M. Hunt, Prevalence and incidence of liver enzyme elevations in a pooled oncology clinical trial cohort, Regul. Toxicol. Pharmacol. 77 (2016) 257–262, https://doi.org/10.1016/j.yrtph.2016.03.019.
[120] V. Kumar, N. Chaudhary, M. Garg, C.S. Floudas, P. Soni, C.B. Chandra, Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy, Front. Pharmacol. 8 (2014) 49, https://doi.org/10.3389/fphar.2017.00049.
[121] E. Björnsson, J. Talwalkar, S. Treeprasertsuk, P.S. Kamath, N. Takahashi, S. Sanderson, et al., Drug-induced autoimmune hepatitis: clinical characteristics and prognosis, Hepatology 51 (2010) 2040–2048, https://doi.org/10.1002/hep.23588.
[122] D. Kleiner, D. Berman, Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma, Dig. Dis. Sci. 57 (2012) 2233–2240, https://doi.org/10.1007/s10620-012-2140-5.
[123] M. Johncilla, J. Misdraji, D.S. Pratt, A.T. Agoston, G.Y. Lauwers, A. Srivastava, et al., Ipilimumab-associated hepatitis: clinicopathologic characterization in a series of 11 cases, Am. J. Surg. Pathol. 39 (2015) 1075–1084, https://doi.org/10.1097/PAS.0000000000000453.
[124] D.E. Kleiner, Drug-induced liver injury: the hepatic pathologist's approach, Gastroenterol. Clin. N. Am. 46 (2017) 273–296, https://doi.org/10.1016/j.gtc.2017.01.004.
[125] I. Spankuch, M. Gassenmaier, I. Tampouri, S. Noor, A. Forschner, C. Garbe, et al., Severe hepatitis under combined immunotherapy: resolution under corticosteroids plus antithymocyte immunoglobulins, Eur. J. Canc. 81 (2017) 203–205, https://doi.org/10.1016/j.ejca.2017.05.018.
[126] T.Z. Horvat, N.G. Adel, T.-O. Dang, P. Momtaz, M.A. Postow, M.K. Callahan, et al., Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center, J. Clin. Oncol. 33 (2015) 3193–3198, https://doi.org/10.1200/JCO.2015.60.8448.
[127] A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, et al., Adjuvant ipilimumab versus placebo after complete resection of high risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial, Lancet Oncol. 16 (2015) 522–530, https://doi.org/10.1016/S1470-2045(15)70122-1.
[128] M. Gauci, B. Baroudjian, C. Zeboulon, C. Pages, N. Poté, et al., Lebbe C for the PATIO group. Immune-related hepatitis with immunotherapy: are corticosteroids always needed? J. Hepatol. 69 (2018) 548–550, https://doi.org/10.1016/j.jhep.2018.03.034.
[129] H.G. Reddy, B.J. Schneider, A.W. Tai, Immune checkpoint inhibitor-associated colitis and hepatitis, Clin. Transl. Gastroenterol. 9 (2018) 180, https://doi.org/10.1038/s41424-018-0049-9.
[130] K.D. Chmiel, D. Suan, C. Liddle, B. Nankivell, R. Ibrahim, C. Bautista, et al., Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy, J. Clin. Oncol. 29 (2011) e237–240, https://doi.org/10.1200/JCO.2010.32.2206.
[131] T. Ahmed, R. Pandey, B. Shah, J. Black, Resolution of ipilimumab induced severe hepatotoxicity with triple immunosuppressants therapy, BMJ Case Rep. (2015) 1–5, https://doi.org/10.1136/bcr-2014-208102.
[132] H.M. McGuire, E. Shklovskaya, J. Edwards, P.R. Trevillian, G.W. McCaughan, P. Bertolino, et al., Anti-PD-1-induced high-grade hepatitis associated with corticosteroid-resistant T cells: a case report, Cancer Immunol. Immunother. 67 (2018) 563–573, https://doi.org/10.1007/s00262-017-2107-7.
[133] C.R. Stroud, A. Hegde, C. Cherry, A.R. Nagash, N. Sharma, S. Addepalli, et al., Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade, J. Oncol. Pharm. Pract. 25 (2019) 551–557, https://doi.org/10.1177/1078155217745144.
[134] M.H. Pollack, A. Betof, H. Dearden, K. Rapazzo, I. Valentine, A.S. Brohl, et al., Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma, Ann. Oncol. 29 (2018) 250–255, https://doi.org/10.1093/annonc/mdx642.
[135] C.M. Hunt, J.I. Papay, V. Stanulovic, A. Regev, Drug rechallenge following drug-induced liver injury, Hepatology 66 (2017) 646–654, https://doi.org/10.1002/hep.29152.